VOLUME 57 • FEBRUARY 1957 • NUMBER 2

A.M.A. ARCHIVES OF

OPHTHALMOLOGY

Electromyography—A Tool in Ocular and Neurologic Diagnosis
Goodwin M. Breinin
I. Myasthenia Gravis
II. Muscle Palsies

Electromyographic Evidence for Ocular Muscle Proprioception in Man
Goodwin M. Breinin

Unilateral Headache and Oculomotor Paralysis Not Caused by Aneurysm
Harvey A. Lincoff and David G. Cogan

Heparin in Senile Macular Degeneration
Sol Rome

An Analysis of the General Type of Uniocular Rotations
Paul Boeder

Lens Metabolism as Studied with the Reversible Cation Shift
Daniel J. Heinrichs and John E. Harris

The Treatment of Trachoma with Subconjunctival Injections of Chloramphenicol
R. W. B. Holland

Vascular Changes in Eyes of Diabetic Rats
Ralph G. Janes and Philip P. Ellis

The Effects of Nutritional and Endocrine Factors on an Inherited Retinal Degeneration in the Mouse
D. R. Lucas and J. P. Newhouse

Mikulicz's Disease of the Lacrimal Gland
D. F. Milam Jr.

The Use of the Antibacterial Drugs and Streptokinase
Joseph M. Miller, David W. Parke, John A. Surmonte, Milton Ginsberg, and Frank B. Ablondi

Localization of Intraocular Foreign Bodies by Roentgen Examination
Fernando E. Rosas

The Role of Intraocular Pressure in the Development of the Chick Eye
Alfred Joseph Coulombre

Fixation Patterns in Strabismic Amblyopia
Paul J. Hauser and Hermann M. Burian

The Hyperbolas of Accommodation and Convergence
Robert V. Hill

Studies on the Glutathione in Bovine Lens
Jin H. Kinoshita and Thomas Masurat

Data Camera for Labeling Ophthalmic Stereograms
Herman J. Norton Jr.

Metastasis of Adenocarcinoma of Colon to Conjunctival Surface of Lid
Paul J. Ostriker

Tabetic Optic Atrophy
Ernest D. Helmick

Ophthalmologic Use of New Stereo Attachment
Theodore N. Zekman

A Fixation Light for Tonometry and Tonography
S. I. Askovitz

Orbitoethmoidal Osteoma
F. J. Damato and T. J. Damato

Cornea and Sclera
Leonard Christensen

Luneburg Theory of Visual Geodesics in Binocular Space Perception
Thorne Shipley and Gordon L. Walker Paul C. Squires

College of Physicians of Philadelphia, Section on Ophthalmology

News and Comment

Books

AMERICAN MEDICAL ASSOCIATION PUBLICATION

maybe you didn't know, Doctor—

H.O.V. HAS A

complete instrument repair service

OUR EXPERT TECHNICIANS WILL—

- clean as well as service those delicate, valuable instruments you use, to give you maximum performance
- provide replacements from our complete stock of domestic and imported instrument parts
- in some cases, provide "loaners" while your own instrument is being serviced or repaired
- guarantee you workmanship backed by a thorough and experienced understanding of the complexities of your instruments
- assure you of the finest service—and the fastest—for replacement of parts, servicing, repairs

THIS IS JUST ANOTHER EXAMPLE OF H.O.V.'S COMPLETE SERVICE TO THE EYE PHYSICIAN

The House of Vision Inc.

Service Department

©H.O.V.

137 NORTH WABASH • CHICAGO, ILLINOIS

TABLE OF CONTENTS

VOLUME 57 FEBRUARY 1957 NUMBER 2

ORIGINAL ARTICLES

PAGE

Electromyography—A Tool in Ocular and Neurologic Diagnosis
Goodwin M. Breinin, M.D., New York
I. Myasthenia Gravis 161
II. Muscle Palsies 165

Electromyographic Evidence for Ocular Muscle Proprioception in Man
Goodwin M. Breinin, M.D., New York 176

Unilateral Headache and Oculomotor Paralysis Not Caused by Aneurysm
Harvey A. Lincoff, M.D., and David G. Cogan, M.D., Boston 181

Heparin in Senile Macular Degeneration
Sol Rome, M.D., Los Angeles 190

An Analysis of the General Type of Uniocular Rotations
Paul Boeder, Ph.D., Southbridge, Mass. 200

Lens Metabolism as Studied with the Reversible Cation Shift
Daniel J. Heinrichs, M.D., and John E. Harris, M.D., Portland, Ore. 207

The Treatment of Trachoma with Subconjunctival Injections of Chloramphenicol
R. W. B. Holland, M.B., Quetta, Baluchistan, Pakistan 214

Vascular Changes in Eyes of Diabetic Rats
Ralph G. Janes, Ph.D., and Philip P. Ellis, M.D., Iowa City 218

The Effects of Nutritional and Endocrine Factors on an Inherited Retinal Degeneration in the Mouse
D. R. Lucas, M.D., and J. P. Newhouse, B.Sc., London, England 224

Mikulicz's Disease of the Lacrimal Gland
D. F. Milam Jr., M.D., Boston 236

The Use of the Antibacterial Drugs and Streptokinase
Joseph M. Miller, M.D.; David W. Parke, M.D.; John A. Surmonte, M.D.; Milton Ginsberg, M.D., Fort Howard, Md., and Frank B. Ablondi, A.B., Pearl River, N. Y. 241

Localization of Intraocular Foreign Bodies by Roentgen Examination
Fernando E. Rosas, M.D., Yucatan, Mexico 245

The Role of Intraocular Pressure in the Development of the Chick Eye
Alfred Joseph Coulombre, Ph.D., New Haven, Conn. 250

Fixation Patterns in Strabismic Amblyopia
Paul J. Hauser, M.D., Evanston, Ill., and Hermann M. Burian, M.D., Iowa City 254

The Hyperbolas of Accommodation and Convergence
Robert V. Hill, M.D., Longview, Wash. 259

Studies on the Glutathione in Bovine Lens
Jin H. Kinoshita, Ph.D., and Thomas Masurat, B.A., Boston 266

Data Camera for Labeling Ophthalmic Stereograms
Herman J. Norton Jr., M.D., Rochester, N. Y. 275

Metastasis of Adenocarcinoma of Colon to Conjunctival Surface of Lid
Paul J. Ostriker, M.D., Stamford, Conn. 279

CASE REPORTS

Tabetic Optic Atrophy
Ernest D. Helmick, M.D., Philadelphia 282

CLINICAL NOTES, NEW INSTRUMENTS AND TECHNIQUES

Ophthalmologic Use of New Stereo Attachment
Theodore N. Zekman, M.D., Chicago 286

A Fixation Light for Tonometry and Tonography
S. I. Askovitz, M.D., Philadelphia 288

REGISTRY OF INTERESTING CASES

Orbitoethmoidal Osteoma
F. J. Damato, F.R.C.S., and T. J. Damato, Floriana, Malta 290

ANNUAL REVIEWS

Cornea and Sclera
Leonard Christensen, M.D., Portland, Ore. 295

CORRESPONDENCE

Luneburg Theory of Visual Geodesics in Binocular Space Perception
Thorne Shipley, Ph.D., and Gordon L. Walker, Ph.D., Southbridge, Mass. 311
Paul C. Squires, Ph.D., New London, Conn. 312

SOCIETY TRANSACTIONS

College of Physicians of Philadelphia, Section on Ophthalmology 315

REGULAR DEPARTMENTS

News and Comment 320
Books 322

A. M. A.
ARCHIVES OF OPHTHALMOLOGY

Continuing the Publication
FOUNDED BY HERMAN KNAPP, 1869

VOLUME 57 FEBRUARY 1957 NUMBER 2

COPYRIGHT, 1957, BY THE AMERICAN MEDICAL ASSOCIATION

EDITORIAL BOARD

FRANCIS HEED ADLER, Chief Editor
313 South Seventeenth Street, Philadelphia 3

W. L. BENEDICT, Rochester, Minn.
DAVID G. COGAN, Boston
JOHN H. DUNNINGTON, New York
MICHAEL J. HOGAN, San Francisco
WILLIAM F. HUGHES Jr., Chicago
KENNETH C. SWAN, Portland, Ore.
WILLIAM ZENTMAYER, Philadelphia

ASSOCIATES:

Crowell Beard
Bernard Becker
F. Phinizy Calhoun Jr.
Leonard Christensen
Zacharias Dische
W. Morton Grant
Albert N. Lemoine Jr.
Donald J. Lyle
John M. McLean
Paul W. Miles
Marshall M. Parks
Henry P. Wagener

AUSTIN SMITH, Editor, A. M. A. Scientific Publications
GILBERT S. COOPER, Managing Editor, Specialty Journals

SUBSCRIPTION RATES

Price per annum in advance, including postage: Domestic, $12.00. Canadian, $12.50. Foreign, $13.50. Price to students, interns, and residents, $7.00 in U. S. & possessions.

Single copies of this and previous calendar year, $1.25.

Checks, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

AMERICAN MEDICAL ASSOCIATION Publication

Published monthly by the AMERICAN MEDICAL ASSOCIATION. Editorial and Circulation Offices: 535 North Dearborn Street, Chicago 10, Illinois. Publication Office: Thompson Lane, Box 539, Nashville 1, Tennessee. Change of Address: Notice to the circulation office should state whether or not change is permanent and should include the old address. Six weeks' notice is required to effect a change of address. Second-class mail privileges authorized at Nashville, Tenn., Aug. 6, 1956.

increasingly preferred

by physicians

strikingly effective

for patients

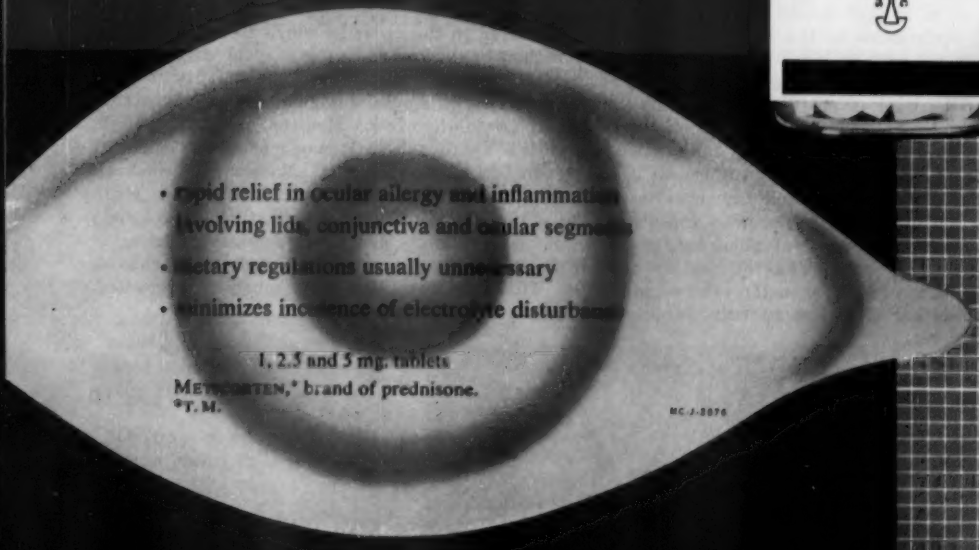
in allergic

and inflammatory

eye disorders

METICORTEN*

(PREDNISONE)



- rapid relief in ocular allergy and inflammation involving lids, conjunctiva and ocular segments
- dietary regulations usually unnecessary
- minimizes incidence of electrolyte disturbance

1, 2.5 and 5 mg. tablets

METICORTEN,* brand of prednisone.
*T. M.

MC J-3876

Instructions to Contributors

Articles, book reviews, and other materials for publication should be addressed to the Chief Editor of the Specialty Journal concerned. Articles are accepted for publication on condition that they are contributed solely to that journal.

An original typescript of an article, with one carbon copy, should be provided; it must be double or triple spaced on one side of a standard size page, with at least a 1-inch margin at each edge. Another carbon copy should be retained by the author. An article in English by a foreign author should be accompanied by a draft in the author's mother tongue. Improvised abbreviations should be avoided.

The main title of an article may not contain more than eighty characters and spaces; a subtitle may be of any length. The subtitle should be sufficiently detached from the main title that a punctuation mark as strong as a colon can be used to separate it from the main title; it must not begin with "with."

The author's name should be accompanied by the highest earned academic or medical degree which he holds. If academic connections are given for one author of an article, such connections must be given for all other authors of the article who have such connections.

If it is necessary to publish a recognizable photograph of a person, the author should notify the publisher that permission to publish has been obtained from the subject himself if an adult, or from the parents or guardian if a child. An illustration that has been published in another publication should be accompanied by a statement that permission for reproduction has been obtained from the author and the original publisher.

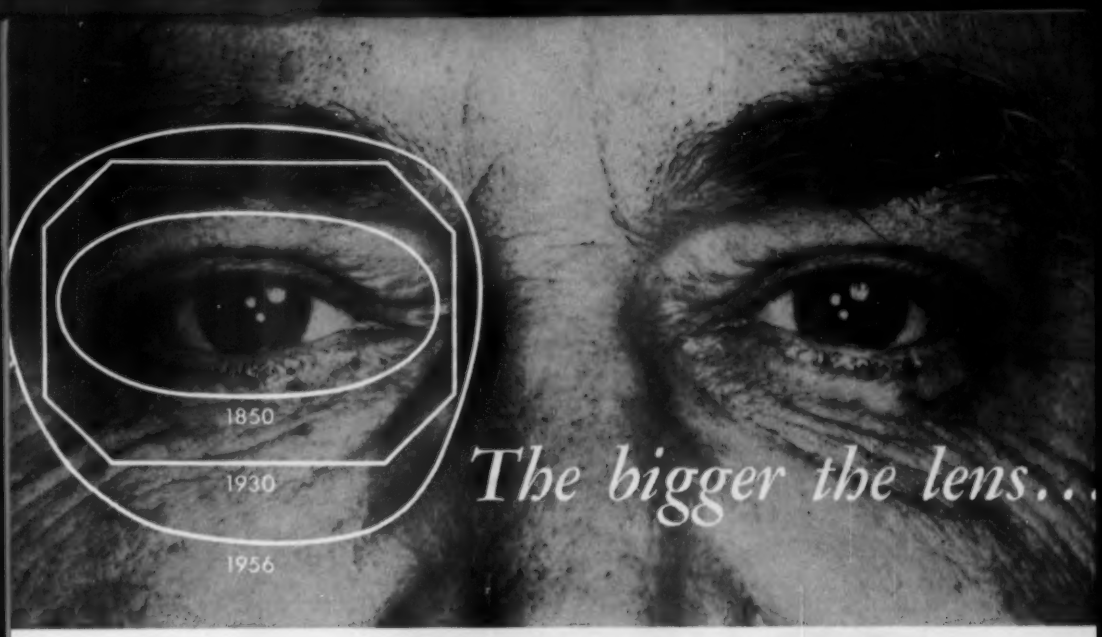
Oversized original illustrations should be photographed and a print on glossy paper submitted. Prints of a bluish tinge should be avoided. Large photomicrograph prints will be reduced in scale unless portions to be cropped are indicated by the author. The author should submit duplicate prints of roentgenograms and photomicrographs with the essential parts that are to be emphasized circled, as a guide to the photoengraver.

Charts and drawings should be in black ink on hard, white paper. Lettering should be large enough, uniform, and sharp enough to permit necessary reduction. Glossy prints of x-rays are requested. Paper clips should not be used on prints, since their mark shows in reproduction, as does writing on the back of prints with hard lead pencil or stiff pen. Labels should be prepared and pasted to the back of each illustration showing its number, the author's name, and an abbreviated title of the article, and plainly indicating the top. Charts and illustrations must have descriptive legends, grouped on a separate sheet. Tables must have captions. ILLUSTRATIONS SHOULD BE UNMOUNTED.

References to the literature should be numbered in the order in which they are referred to in the text or listed in alphabetical order without numbers. A chronological arrangement, with all entries for a given year alphabetized according to the surname of the first author, may be used if preferred. References should be typed on a special page at end of manuscript. They should conform to the style of the Quarterly Cumulative Index Medicus, and must include, in the order given, name of author, title of article (with subtitle), name of periodical, with volume, page, month—day of month if weekly or biweekly—and year. Names of periodicals should be given in full or abbreviated exactly as in the Quarterly Cumulative Index Medicus. Reference to books must contain, in the order given, name of author, title of book, city of publication, name of publisher, and year of publication. Titles of foreign articles, if originally in a generally known Romance or Germanic tongue, must either all be in English translation or all be in the original language. Titles in other languages must be translated. The author must assume responsibility for the accuracy of foreign titles.

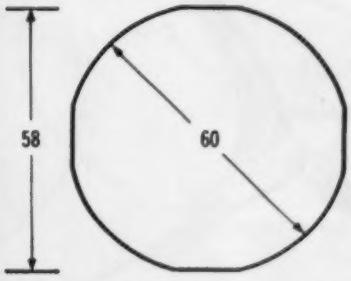
AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **Chicago 10**



...the greater the need *for* ORTHOGON!

NOW...Orthogon correction in 95% of single vision prescriptions *without second-side surfacing!*



Now Orthogon uncuts are available in 58 × 60mm size. This means economy and quicker service. Even the most outsized modern shapes are supplied from Orthogon uncuts—with good glass left to spare.

Modern eyewear demands ever bigger lenses. And, of course, the only way to make them bigger is to add more glass at the margin. ***How important it becomes that your patients get the benefit of Orthogon marginal correction!*** To achieve the best possible end result of all your professional skill, insist on the highest order of quality in the lenses you prescribe. Insist on Orthogon—in *any* dresswear size.

BAUSCH & LOMB

SINCE 1853

11
TEN

MILLION, THANKS...

YES, the *total* has changed . . . Browline® frames have passed the eleven million mark, thanks to their still increasing preference.

The *reasons* for preferring Browlines have not changed—their advantages in patient approval of their styling and comfort . . . ease in fitting . . . interchangeability . . . readily available styles, colors and sizes—in depth . . . dependable quality . . . plus the fact they're 'SHURON.'

In your choice of lenses, cases, and machinery, too, "the swing is to Shuron." Your 1955 orders exceeded those of 1954 by more than 20% . . . and are even higher this year.

We appreciate your preference . . . a preference that makes Shuron the world's largest organization devoted exclusively to serving the ophthalmic profession.

SHURON OPTICAL COMPANY, INC. SHURON® **Geneva, N.Y. Rochester, N.Y.**

Clement Clarke *of England . . .*

THE MAJOR SYNOPTOPHORE

An Entirely New Major Amblyoscope

It is with great pleasure that we announce the introduction of an entirely new Major Amblyoscope, which we have named the MAJOR SYNOPTOPHORE in order to perpetuate a name so long associated with this house.

The Major Synoptophore is the result of several years of research into the needs of the Orthoptic Technician. We are grateful to the very many Orthoptists, in the United Kingdom, the United States of America, the Continent of Europe and indeed in all parts of the world, who have cooperated with us and made this instrument a possibility.

A comprehensive leaflet is now in the course of production and we shall be pleased to mail this to enquirers. Meanwhile, however, we summarise a few of the inovations of this first class, up to date strabismus apparatus:—

A MODERN DESIGN WHICH LOOKS AS GOOD AS IT FEELS TO OPERATE
SUFFICIENT STRENGTH TO WITHSTAND THE GREAT AMOUNT OF USE TO WHICH IT WILL BE SUBJECTED
INCORPORATION OF "AFTER-IMAGE" TEST
INCORPORATION OF AUTOMATIC FLASHING UNIT
HOUSING OF THE TRANSFORMER INSIDE THE INSTRUMENT
MANY IMPROVEMENTS SUCH AS GREATER RANGE OF CHINREST HEIGHT, I.P.D. SCALE ON ORTHOPTIST'S SIDE, DUCTIONS SCALES IN DEGREES FOR EASIER MEASUREMENTS, LARGE BREATHSHIELD, SILENCE OF MOVEMENT, ETC.

CLEMENT CLARKE

63 WIGMORE STREET • LONDON • W.1. ENGLAND

We shall welcome the opportunity of quoting you and sending you all the details you require, both in respect of this instrument and any others of our large range

proved... in industrial eye practice

SODIUM SULAMYD

ophthalmic preparations

Schering

Standard for over a decade for prevention and treatment of eye infections

More than a decade of use confirms these advantages of Sodium SULAMYD in the treatment and prophylaxis of ocular infections:

- Rapid absorption—excellent penetration of ocular tissues.
- Promptly effective against all common eye pathogens—both gram positive and gram negative.
- Minimizes incidence of infection after ocular trauma.
- Little tendency to bacterial resistance.
- Nonirritating to eye—virtual absence of sensitivity reactions.
- Repeatedly endorsed for industrial eye practice.[1-3]

THREE FORMS FOR YOUR CONVENIENCE:

Sodium SULAMYD Ophthalmic Solution 30%—*for severe infections*: 5 cc. and 15 cc. dropper bottles.

Sodium SULAMYD Ophthalmic Solution 10% with Methylcellulose 0.5%—*for mild and moderately severe infections and prophylaxis*: 15 cc. dropper bottle.

Sodium SULAMYD Ophthalmic Ointment 10%—*for nighttime use and for treatment of styes and lid infections*: ⅛ oz. tube.

References: (1) Dickson, R. M.: Brit. J. Phys. Med. *7*:77, 1944. (2) Collier, E.: Brit. J. Phys. Med. *6*:181, 1943. (3) Mayer, L. L.: A.M.A. Arch. Ophth. *39*:232, 1948.

SS-J-117

Sodium SULAMYD,® brand of Sulfacetamide Sodium U.S.P.

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

This fall and winter...prescribe Benson's

ALL AMERICAN* ATHLETIC GLASSES

Designed for rough treatment

Your athlete patients will receive maximum comfort and protection during competition if they wear **ALL AMERICAN* ATHLETIC GLASSES** . . . practical and useable on all noses for almost every sport.

Extra sturdy all-metal frame
"Cushion Fit" shock absorbent rubber nose piece
Ends and temples covered to protect other players
Expansible, adjustable "Glass-Gard"* headband
Drop-ball tested safety precision lenses

Prices on request. A complete sample may be ordered at nominal cost from your supplier or BENSON OPTICAL COMPANY.

For your protection and ours, look for the trademark AA on the lenses of every pair of **ALL AMERICAN* ATHLETIC GLASSES**

*Copyright

Since 1913

Benson OPTICAL COMPANY

Executive Offices • Minneapolis, Minn.

LABORATORIES CONVENIENTLY LOCATED IN UPPER MIDWEST CITIES

new needle sutures

for scleral resection and dacryocystorhinostomy

double-armed ophthalmic needle-sutures with special MICRO-POINT® needles designed in consultation with leading ophthalmologists for use in particularly delicate procedures.

ETHICON®

does WHAT YOU WANT A GOOD TOPICAL ANESTHETIC TO DO

doesn't DO WHAT YOU'RE AFRAID SUCH A POTENT AGENT MIGHT DO

Criteria of the ideal topical anesthetic[1]	Evaluation of DYCLONE by these criteria
RAPID EFFECT	Dyclone is a rapid acting local anesthetic.[1]
HIGH POTENCY	Dyclone has a high degree of potency.[1-3]
SAFETY	Large areas can be treated without danger; notably safe even if complete absorption is assumed.[1]
LOW SENSITIZING POTENTIAL	In more than 5,000 reported cases sensitization to Dyclone was less than 0.1%. No instance of cross sensitization with other topical anesthetics was found.[5]
NO IRRITATION	Dyclone is "... effective without frequent irritation."[2]

references: 1. Arora, R. B., et al.: E.E.N.T. Monthly 34: 593, 1955. 2. Hungerford, L. N.: Bull. Mason Clin. 9: 105, 1955. 3. Shelmire, B.; Gastineau, F. M., and Shields, T. L.: Arch. Dermat. 71: 728, 1955. 4. Morginson, W. J., et al.: Postgrad. Med. 19: 605, 1956. 5. Data from Pitman-Moore Research Files.

Dyclone™ IN OPHTHALMOLOGY

dyclonine hydrochloride

the entirely NEW topical anesthetic with antibacterial properties

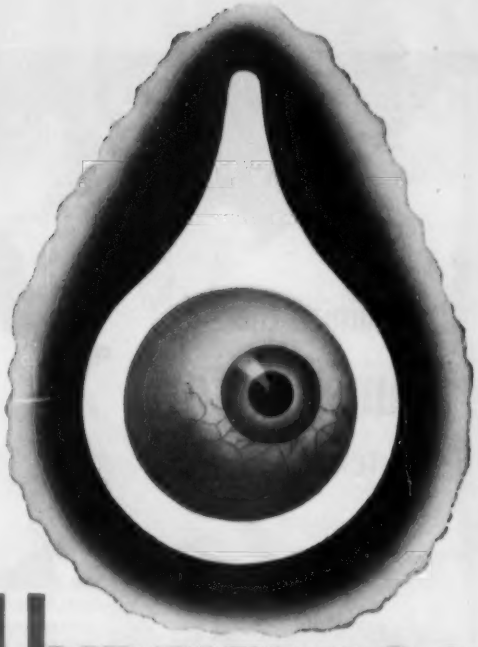
supply:
Dyclone Creme, in 1 oz. tubes.
Dyclone Solution, in 1 and 8 oz. bottles.

Write for literature and samples

Pitman-Moore Company *Division of Allied Laboratories, Inc.* • **Indianapolis 6, Indiana**

NEW

True solution
assures
maximum
anti-inflammatory
benefits



STERILE
OPHTHALMIC
SOLUTION

'NEO-HYDELTRASOL'

(PREDNISOLONE 21-PHOSPHATE-NEOMYCIN SULFATE)

Now you can offer your patient needing topical therapy the *unsurpassed benefits* of the first stable, sterile soluble "predni-steroid" *in true solution.* Sterile Ophthalmic Solution 'NEO-HYDELTRASOL' contains a soluble inorganic ester of the potent "predni-steroid"—prednisolone 21-phosphate. 'NEO-HYDELTRASOL' provides *these important advantages:*

- **freedom from any particulate matter capable of injuring ocular tissues.**
- **uniform and effective concentrations of prednisolone.**
- **compatibility with ocular tissues and fluids.**
- **stability for long periods (does not need refrigeration).**

Indications: Allergic and inflammatory lesions of the anterior segment; injury due to physical or chemical trauma.

Contraindications: Ocular herpes simplex and ocular tuberculosis.

Supplied: *Sterile Ophthalmic Solution* 'NEO-HYDELTRASOL'—*each cc. contains 5 mg. (1%) prednisolone 21-phosphate (as sodium salt) and 5 mg. Neomycin Sulfate (equivalent to 3.5 mg. neomycin base); 5-cc. vials.*

MSD

MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC. PHILADELPHIA 1, PA.

with

cyclogyl® *hydrochloride*

brand of cyclopentolate hydrochloride

Rapid onset of action,[1,2] brief duration,[1,3] and consistent depth of cycloplegia make Cyclogyl ". . . [a] drug of choice for routine refraction."[1]

Cyclogyl does not produce local or systemic toxic effects, and is relatively nonirritating and nonsensitizing;[3,4] *it has not been reported to cause a significant variation in intraocular tension.*[4,5] Cyclogyl is effective in highly pigmented eyes, and may be used for persons of all ages.[4] No pretreatment is required.

Just one or two drops provides complete cycloplegia, thereby conferring a saving in medication cost.

Send for literature and samples

Indications: Refraction; as a mydriatic in controlling iritis, iridocyclitis, keratitis, and choroiditis; to prevent lenticular adhesions; with miotics for preventing or breaking adhesions in infection; preoperatively, for cataract or other appropriate eye surgery.

Supplied: 0.5% Solution in 15 cc. dropper bottles; 1% Solution in 2 cc. and 15 cc. dropper bottles.

*When a miotic is used. Otherwise, in less than 20 hours.

1. Rasgorshek, R. H. and McIntire, W. C.: Am. J. Ophth. 40:34 (July) 1955. • 2. Ehrlich, L. H.: N. Y. State J. Med. 53:3015 (Dec. 15) 1953. • 3. Gettes, B. C.: A.M.A. Arch. Ophth. 51:467 (April) 1954. 4. Council on Pharmacy and Chemistry: J.A.M.A. 158:1523 (Aug. 27) 1955. • 5. Stolzer, I. H.: Am. J. Ophth. 36:110 (Jan.) 1953.

Schieffelin & Co. / Since 1794

PHARMACEUTICAL AND RESEARCH LABORATORIES

28 Cooper Square, New York 3, N.Y.

In Canada:
W. Sofin Ltd., Montreal 25, Quebec

A.M.A. ARCHIVES OF
OPHTHALMOLOGY

Electromyography—A Tool in Ocular and Neurologic Diagnosis

I. Myasthenia Gravis

GOODWIN M. BREININ, M.D., New York

The application of electrophysiologic techniques to the analysis of ocular motility problems has yielded important information and provided a most useful tool for diagnosis and research in related fields of ophthalmology and neurology.[1-3]

Our understanding of normal patterns of innervation of the extraocular muscles has been advanced, and considerable insight has been obtained in the altered dynamics of ocular muscle pareses, myopathies, ptosis, myasthenia gravis, comitant strabismus, and nystagmus. The effect of drugs may be readily evaluated.

The technique requires the subconjunctival insertion of fine-gauge concentric electrodes directly into the extraocular muscles, using only topical anesthesia. This is a simple, practical procedure, devoid of harmful effects—the only complication is the occasional occurrence of a subconjunctival ecchymosis which is a cosmetic blemish of brief duration. The muscle potentials are suitably amplified, displayed on dual beam oscilloscopes, and recorded with moving film photography. Extraocular muscle motor units have a duration of only 1 to 2 milliseconds (evidence of the small innervation ratio) and an amplitude of 20μv to 600μv and can recruit at high frequency.

The usefulness of electromyography has been made evident in the following observations.

Received for publication June 19, 1956.

Presented before the New England Ophthalmological Society, Boston, Feb. 15, 1956.

From the Department of Ophthalmology of the New York University Post-Graduate Medical School.

Studies conducted under Grant B-911 of the National Institute of Neurological Diseases and Blindness and under grants from the National Council to Combat Blindness and the Stanley Tausend Foundation.

A Test for Myasthenia Gravis

Involvement of the extraocular muscles has long been noted as among the earliest evidences of this disabling and often fatal disease. The muscle weakness may be controlled with certain anticholinesterase or anticurare type drugs (neostigmine, tetraethylpyrophosphate [TEPP], octamethyl pyrophosphoramide [OMPA], edrophonium, etc). The response of the myasthenic muscle to these drugs has been of great diagnostic as well as therapeutic value and is widely employed for these purposes. The clinical evidences of response are improvements in motility of the paretic muscles on exhibition of the drug. Unfortunately, this improvement may be only minimal or equivocal so that diagnosis remains in doubt. The utilization of electromyography to evaluate drug action has revealed a striking and characteristic muscle response even though

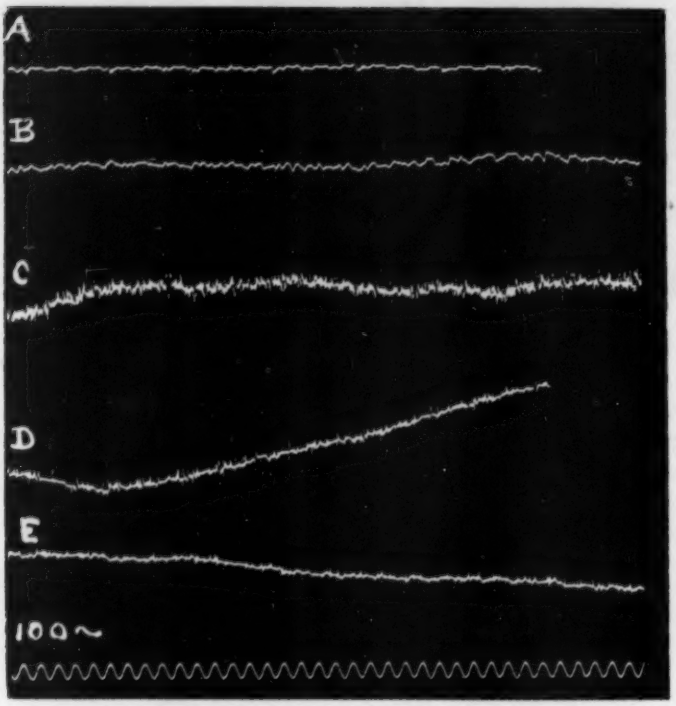


Fig. 1. — Electromyogram of levator and lateral rectus in myasthenia. *A*, levator, single unit. *B*, lateral rectus, low-grade activity. *C*, 30 seconds after edrophonium, abundant activity. *D*, one minute later. *E*, two to three minutes later. Amplitude of time signal, 100μv.

gross improvement of motility may not be evident. The best drug for this purpose is edrophonium (Tensilon chloride), which has the virtue of rapid action although very brief duration. Introduced as an anticurare agent,[4] it was subsequently applied therapeutically, but with disappointing results owing to its short action. It has been advocated for diagnosis and as a guide to therapeutic management of the myasthenia patient.[5-8] For these purposes the electromyographic evaluation of drug action has much to recommend it and may prove to be the best approach, as seen in the following cases.

Case 1.—The patient had a long history of vague weakness, variable ptosis, and diplopia. He exhibited ptosis and inability to turn both eyes to the right (gaze palsy). Gross response to neostigmine and edrophonium was equivocal. In fact, the question of hysteria was raised. The ptosis improved somewhat but not the gaze palsy. Peripheral muscular weakness was benefited moderately. Electromyography, however, revealed a marked motor unit response in the extraocular muscles. Prior to intravenous injection of 1 cc. (10 mg.) of edrophonium chloride the levator was firing only a single unit on maximum effort at elevation of the lid (Fig. 1*A*). The external rectus had a very low amplitude discharge (Fig. 1*B*). Thirty seconds after injection the levator and external rectus (Fig. 1*C*) fired profusely, although not as much as in the normal. The discharge quickly fell off (one minute, Fig. 1*D*), (two to three minutes, Fig. 1*E*). During this time, despite maximum effort at turning the eyes to the right, practically no movement resulted. The lid did elevate several millimeters. The loss of response was revealed in the gradual falling out of units until the profuse discharge reverted to the previous baseline.

In a later examination, where moderate lid action was present, electromyography without drugs showed a typical fatigue phenomenon, wherein sustained effort at elevat-

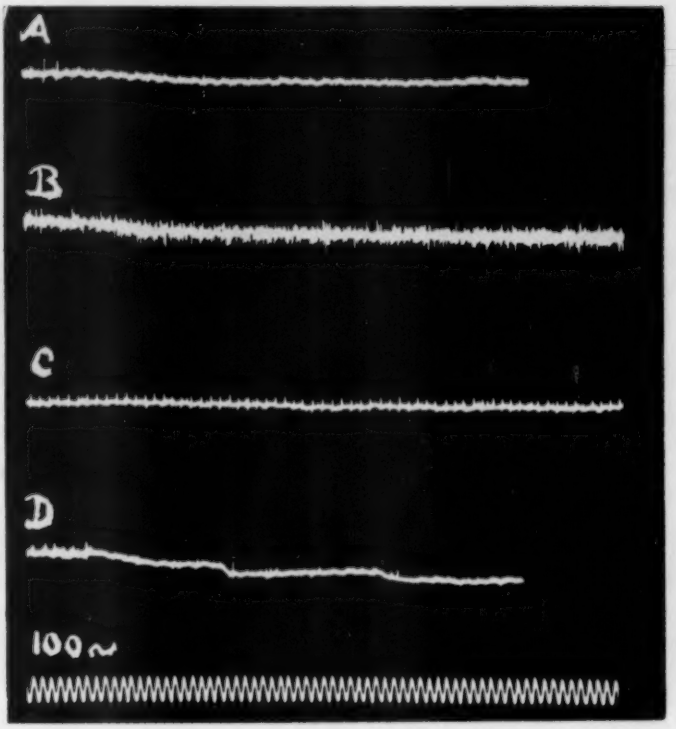


Fig. 2.—Electromyogram of lateral rectus in myasthenia. *A*, lateral rectus, almost silent. *B*, 30 seconds after edrophonium, abundant discharge. *C*, single unit discharge, one minute later. *D*, two to three minutes later, reverting to baseline. Amplitude of time signal, 100μv.

ing the lid resulted in a progressive falling out of units—like a forest being reduced to a few trees.

CASE 2.—For five years the patient had variable bilateral ptosis and intermittent diplopia with peripheral weakness. He exhibited bilateral ptosis and limited ocular movement in all directions, most marked in gaze to the right. The ptosis improved markedly with edrophonium. Electromyography of the external rectus showed an almost silent tracing (Fig. 2*A*). Thirty seconds after 1 cc. of edrophonium chloride the muscle fired profusely, although at less than normal amplitude (Fig. 2*B*). About one minute later the discharge had fallen off to a few rhythmic motor units (Fig. 2*C*). In two to three minutes the tracing showed the baseline level (Fig. 2*D*). The eye did not turn out more than a degree or two despite maximum effort following injection of the drug.

Comment

Intravenous injection of saline substituted for edrophonium without the knowledge of the patients elicited no response.

The electromyographic study of extraocular muscles reveals characteristic patterns of innervation and response to drugs in myasthenia gravis. In my limited experience there have been no responses of the above type in nonmyasthenic palsies or progressive nuclear ophthalmoplegia or in the normal subject, although it has been reported[5] that edrophonium may cause mild, transient increase of strength in the normal and in some nonmyasthenic diseased muscle. A patient with neurogenic ptosis and a partial third nerve palsy developed sustained fibrillations and fasciculations (10 to 15 minutes) of the levator following edrophonium injection (Fig. 3). The electromyographic tracing of this response was entirely different from that of myasthenia and showed no relation to volition.

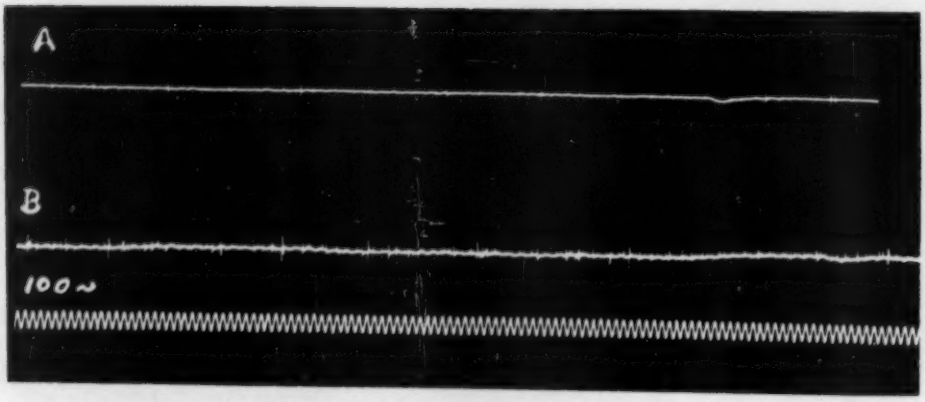


Fig. 3.—*A*, levator palpebrae, paretic. Tiny potentials (fibrillation). *B*, fasciculations and fibrillations induced by edrophonium. Amplitude of time signal, 100μv.

It is of interest that a progressive decrease in amplitude of motor units on sustained effort, such as has been described for peripheral muscle in myasthenia, has not been noted in extraocular muscle. It is probable that anatomic and pharmacologic uniformity of the muscle fibers and the small innervation ratio result in simultaneous, total exclusion of all the muscle fibers of a unit—hence loss of the complete unit—rather than in a unit of decreased amplitude due to inactivation of individual muscle fibers.

Further experience is necessary to establish the specificity of the reaction, but it appears that extraocular muscle electromyography provides a most useful test for the diagnosis and evaluation of therapeutic agents in myasthenia gravis. The following dosage schedule of edrophonium chloride, recommended by Osserman and Teng,[8] should prove valuable in limiting false negative responses (cholinergic reactions) of hyperreactive myasthenic patients: Adults: 0.2 cc. (2 mg.) intravenously over 15 seconds; if no response in 30 seconds, administer 0.8 cc. (8 mg.) more. This important paper should be consulted for details.

550 First Ave. (16).

REFERENCES

1. Bjork, A.: Electromyographic Study of Conditions Involving Limited Mobility of the Eye Chiefly Due to Neurogenic Pareses, Brit. J. Ophth. 38:528, 1954.

2. Breinin, G. M., and Moldaver, J.: Electromyography of the Human Extraocular Muscles: I. Normal Kinesiology; Divergence Mechanism, A. M. A. Arch. Ophth. 54:200, 1955.

3. Breinin, G. M.: The Nature of Vergence Revealed by Electromyography, A. M. A. Arch. Ophth. 54:407, 1955.

4. Macfarlane, D. W.; Pelikan, E. W., and Unna, K. R.: Evaluation of Curarizing Drugs in Man: V. Antagonism to Curarizing Effects of d-Tubocurarine by Neostigmine, m-Hydroxy Phenyltrimethlammonium and m-Hydroxy Phenylethyldimethylammonium, J. Pharm. & Exper. Therap. 100:382, 1950.

5. Westerberg, M. R.; Magee, K. R., and Shideman, R. E.: Effect of 3-Hydroxy-Phenyldimethylethylammonium Chloride (Tensilon) in Myasthenia Gravis, Univ. Michigan M. Bull. 17: 311, 1951.

6. Boruchoff, S. A., and Goldberg, B.: Edrophonium (Tensilon) in Diagnosis of Ocular Myasthenia Gravis, A. M. A. Arch. Ophth. 53:718, 1955.

7. Osserman, K. E.; Kaplan, L. I., and Besson, G.: Studies in Myasthenia Gravis: Edrophonium Chloride (Tensilon) Test as a New Approach to Management, J. Mt. Sinai Hosp. 20: 165, 1953.

8. Osserman, K. E., and Teng, P.: Studies in Myasthenia Gravis—A Rapid Diagnostic Test: Further Progress with Edrophonium (Tensilon) Chloride, J. A. M. A. 160:153, 1956.

Electromyography—A Tool in Ocular and Neurologic Diagnosis

II. Muscle Palsies

GOODWIN M. BREININ, M.D., New York

Electromyography (EMG) of the extraocular muscles has afforded insight into innervational patterns of common and uncommon diseases affecting ocular motility. The method has been described previously.[1,2] The following applications are of particular interest.

A. Neurogenic Palsies of Extraocular Muscles

1. Third, fourth, and sixth nerve palsies are frequently encountered in ophthalmological and neurological practice. It is of diagnostic and prognostic importance to establish the site and character of the lesion. Electromyography has an important role to play in such studies. The following observations considerably amplify the findings of Bjork.[3] The presence of lower motor neuron denervation may be determined. The cardinal sign of denervation is fibrillation—the minute discharge of single muscle fiber potentials which occur spontaneously without relation to volition and indicate lower motor neuron damage. Characteristic fibrillations have been noted in oculomotor palsies.[1] Caution is necessary in the interpretation of ocular muscle potentials, since small, single motor units bear a very close resemblance to fibrillations. In the absence of volitional potentials there is no difficulty in classifying fibrillation, but where volition is present the diagnosis must be restricted to the spontaneous potentials occurring when the gaze is directed out of the field of the affected muscle. The finding of denervation phenomena indicates a protracted recovery—if any. It should be emphasized that fibrillations are infrequently encountered in extraocular muscle palsies.

Furthermore—and this is most important—the EMG pattern of mild palsies is indistinguishable from the normal. Except in complete conduction block or total denervation, some volitional discharge is always present in the paretic muscle. Neurogenic paresis of moderate to severe degree, however, is indicated by irregular or sparse recruitment, poorly sustained discharge (Fig. 1*A* and *B*), and loss of the "interference" pattern characteristically seen on effort, the occurrence of single unit discharges in the field of action of a muscle (Fig. 2*A*, *B*, and *C*) (evidence of the loss of motor units), and denervation fibrillations (Fig. 3). The motor units in a severe paresis of extraocular muscle are usually of decreased amplitude.

Polyphasic motor units have been encountered infrequently in the extraocular muscles, e. g., in a lateral rectus recovering from an abducens palsy (Fig. 4). Polyphasic waves occur often in paretic peripheral skeletal muscle and are thought to be due to temporal or spatial dispersion of the nerve action current resulting in asynchronous discharge of the many muscle fibers of a unit. Their relative rarity reflects the anat-

Received for publication June 19, 1956.

Presented before the New England Ophthalmological Society, Boston, Feb. 15, 1956.

From the Department of Ophthalmology of the New York University Post-Graduate Medical School.

Studies conducted under Grant B-911 of the National Institute of Neurological Diseases and Blindness and under grants from the National Council to Combat Blindness and the Stanley Tausend Foundation.

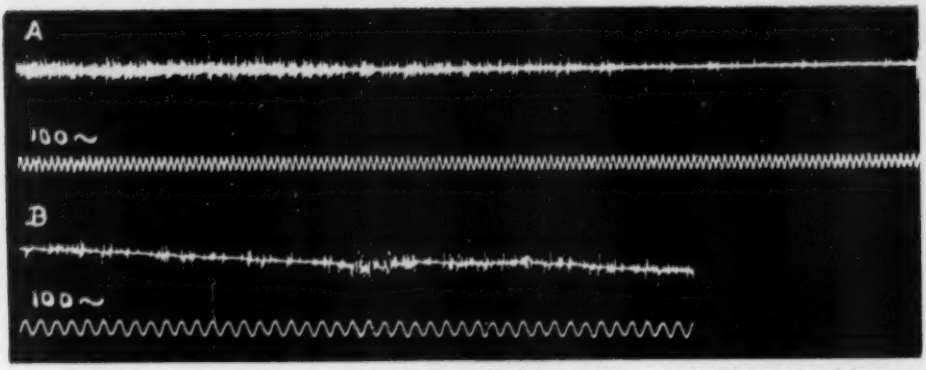


Fig. 1.—Paretic medial rectus. *A*, good activity but poorly sustained. *B*, irregular firing, one nystagmus burst. The amplitude of the time signal is 100μv in every Figure.

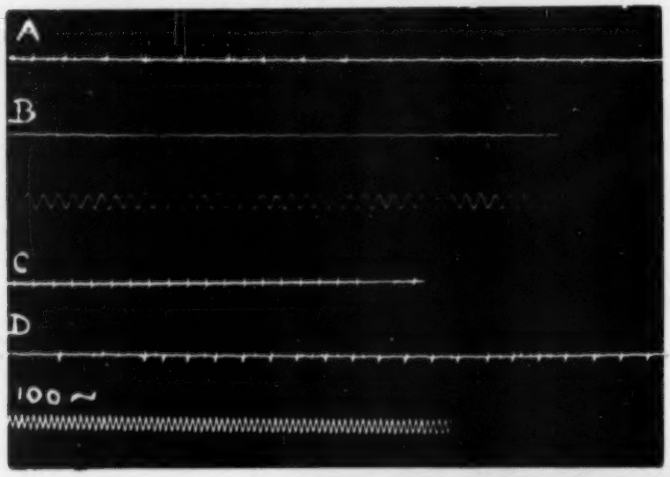


Fig. 2.—Paretic medial rectus. *A*, scanty low-amplitude discharge, possible fibrillations. *B*, a tiny rhythmic motor unit. *C*, single motor units in field of activity of muscle. *D*, volume configuration in single motor unit.

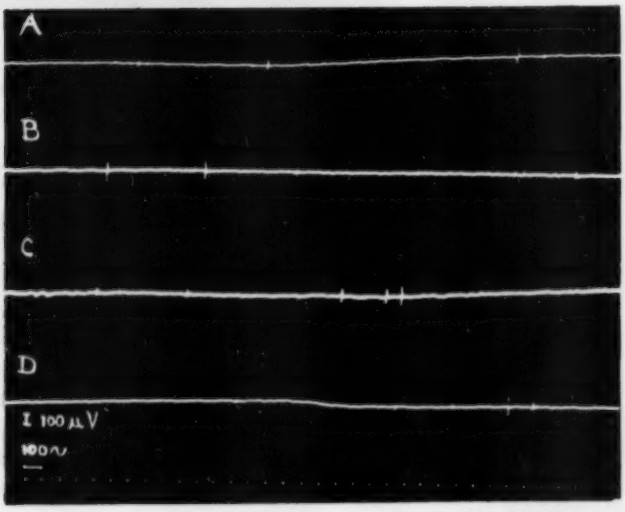


Fig. 3.—Complete third nerve palsy. *A* and *B*, levator fibrillation. *C* and *D*, medial rectus fibrillation.

omic uniformity and low innervation ratio characterizing eye muscles. (Rhythmic discharges of coupled or duplex units during sleep and in palsies have been noted [Fig. 17][4] The occurrence of volume effects in conduction produces typical wave forms of source-sink-source type when the electrode is located at the mid-point in volume [Fig. 2*D*].)

In the case of the orbicularis oculi polyphasic units have been recorded during the recovery reinnervation following Bell's palsy (Fig. 5). This reflects the intermediate position this muscle holds between extraocular and peripheral skeletal muscle. Fibrillations and slow positive waves also were present mingled with normal motor units (Fig. 6). The clinical improvement of this patient during a period of a year has been reflected in the changing EMG patterns in which the normal wave forms have increased and the abnormal have

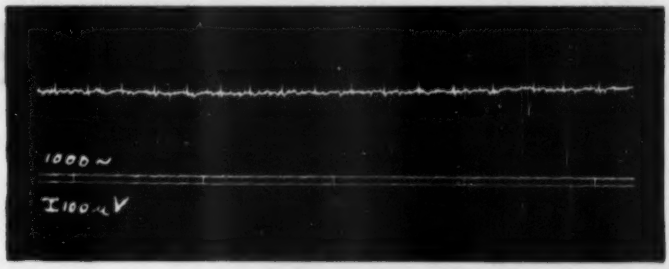


Fig. 4.—Paretic lateral rectus, recovering. Polyphasic motor units, a rarity in ocular muscle (polyphasic unit and single motor unit alternating).

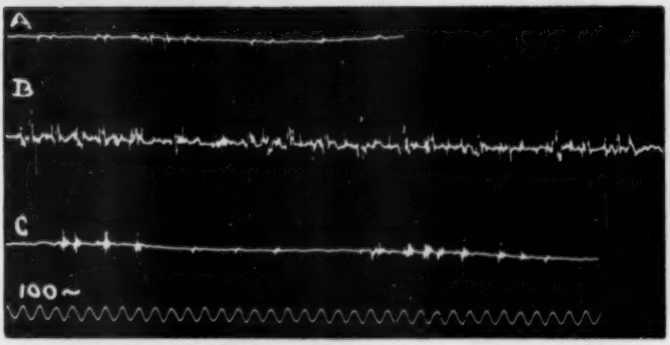


Fig. 5.—Orbicularis oculi, Bell's palsy. *A*, polyphasic units. *B*, polyphasic units and normal units. *C*, polyphasic units.

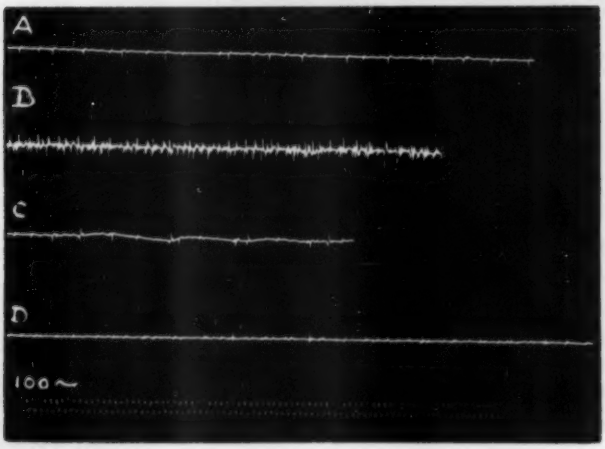


Fig. 6.—Orbicularis oculi, Bell's palsy. *A*, spontaneous activity in muscle. *B*, maximum effort of contraction shows sparse discharge. *C*, spontaneous abnormal activity. *D*, fibrillations.

decreased. The prognostic value of electromyography is thus clearly evident.

2. Pseudoparesis. The occurrence of apparent paresis due to anomalies or disturbances of the antagonist is not infrequent. In general, this type of disorder can be recognized by the limited motility shown by the forced duction test. Electromyography has proved useful in a number of such cases in establishing that the apparently paretic muscle had a normal innervational pattern. One such patient, diagnosed as having a case of complete abducens palsy, showed a large monocular esotropia and amblyopia with practically no abduction movement of the eye. Forced duction showed anatomic obstruction to abduction. Electromyography exhibited a normal level of firing in the lateral rectus. At surgery a large medial rectus recession was carried out. Numerous abnormal fascial bands were encountered surrounding the muscle and were severed. It had originally been planned to do a recession-resection, but in view of the EMG record no surgery was performed on the lateral rectus. The postoperative alignment was very good, the eye being slightly esotropic. Abduction of some 20 degrees was now obtainable.

3. Primary and secondary deviations and overactions have been determined electromyographically.[2] Recently two cases of what appears to be primary spastic esotropia have been studied. These adult patients developed marked comitant esotropia, with no known antecedent muscle imbalance. The apparently paretic lateral recti fired in a completely normal manner, whereas the medial recti exhibited remarkably high amplitude and frequency (reaching almost 1 mv.).

4. Duane's retraction syndrome. The classical description of the congenital retraction syndrome of Duane includes complete absence of abduction, normal or somewhat impaired adduction often accompanied by an upshoot or downshoot of the eye, ptosis and retraction of the globe on adduction, and widening of the palpebral fissure on attempted abduction.

The retraction has generally been considered to result from the pull of the medial rectus against a fibrotic, inelastic lateral rectus which, since it cannot reciprocally relax, results in the globe being pulled backward into the orbit. The ptosis is thought to be a mechanical consequence of the loss of support due to the retraction.

Surgical exposure of the lateral rectus has confirmed the existence of muscle pathology in some patients. In others, it has been reported that the lateral rectus appeared normal whereas the medial rectus exhibited anomalous fascial bands or connections which resulted in the same clinical picture (Gundersen[5]). Scobie[6] has also described the occurrence of medial rectus abnormalities in some cases and classified the retraction syndrome into several types, depending on whether the lateral or medial rectus is primarily involved.

Electromyography was performed in the following cases:

Case 1.—A 30-year-old white man had a retraction syndrome O. S. noted since birth. There was absent abduction and limited adduction with upshoot. The palpebral fissure widened on attempted abduction, and ptosis occurred on adduction, during which retraction of the globe was evident. Thorough exploration of the lateral rectus with the concentric electrode revealed almost no innervation (Fig. 7*A*) except in one needle site, which discharged well. The needle transmitted a sensation of almost gritty resistance. The medial rectus fired normally, as did the levator. Widening of the fissure was accompanied by slightly larger bursts in the levator (Fig. 7*B*). Very little difference was noted in the levator discharge level between the primary position and adduction.

Surgical exploration of the horizontal recti revealed a fibrotic, cord-like lateral rectus, which limited adduction. The medial rectus was essentially normal. In this case the classical explanation for the retraction syndrome was confirmed. There is no

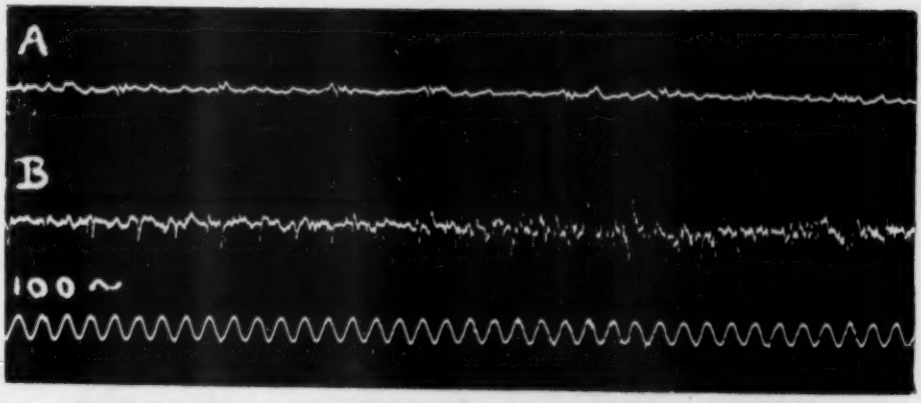


Fig. 7.—Duane's syndrome. *A*, lateral rectus, low-grade activity in primary position and attempted abduction. *B*, levator activity increases on attempted abduction.

doubt, however, that a similar clinical picture can result from disturbances of the medial rectus. Electromyography often can establish the existence and locus of muscle pathology. Normal discharges will be encountered where the disturbance is of an anatomical nature involving adjacent structures, such as aberrant slips, fascial bands, etc.

Case 2.—A 45-year-old man had a typical retraction syndrome O. S. since birth. Binocular vision was present in the primary position. Electromyography recorded no spontaneous firing in the lateral rectus O. S. except in one needle position. The discharges were of low amplitude. No recruitment occurred in gaze left; however, anomalous recruitment occurred in gaze right, out of the field of the muscle (Fig. 8). This phenomenon (in paretic muscles) has been described at length in another report and is due, in my opinion, to a stretch reflex made manifest by the paresis. The discharge became maximal in extreme gaze right but never attained a normal amplitude. In this patient passive rotation did not elicit a discharge from the muscle.

Right nystagmus (optokinetic and caloric) was elicited and showed a fast component to the right in the lateral rectus. Left nystagmus elicited no discharge from the lateral rectus. It should be noted that no discharge or movement could be elicited into the field of the muscle but only out of the field. The possible contribution of this type of anomalous cocontraction to retraction of the globe immediately presents itself. However, in other types of palsies

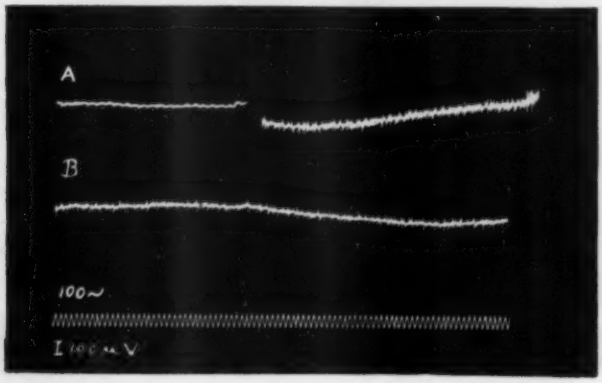


Fig. 8.—Duane's syndrome, lateral rectus. *A*, On left, no activity in primary position or attempted abduction; on right, anomalous recruitment on adduction. *B*, anomalous recruitment.

showing this phenomenon no retraction was noted. It is possible that a small amount of retraction may have occurred in these but was overlooked. The fact that the phenomenon of anomalous innervation has been noted only in neurogenic palsies thus far suggests but does not prove that the basic disturbance in this patient was a neurogenic lesion.

It is clear that this lateral rectus had some muscle fibers which were capable of being discharged and not a general fibrosis.

Unfortunately, this technique is not yet suitable for use in children and is thus limited to cooperative teen-agers or adults. It is hoped that this major impediment to study of the important childhood group of motility disorders will be circumvented in the future.

5. Aberrant third nerve regeneration. The syndrome of aberrant third nerve regeneration is frequently observed to follow an oculomotor palsy. The studies of Bender and Fulton indicated that misdirection of regenerating nerve fibers could explain the clinical findings. Anomalous central connections have also been considered. In fullest manifestation the syndrome consists of retraction of the upper lid, adduction of the globe, and miosis on attempt at looking up, down, or in. From experimental lesions in the monkey Bender and Fulton concluded that random misdirection of a regenerating third nerve results in fibers for all components of the nerve being distributed to all the muscles innervated. On any attempted movement except abduction the antagonistic vertical muscles are simultaneously innervated and thus neutralize each other, whereas the unopposed medial rectus, levator, and sphincter pupillae account for the adduction, lid retraction, and miosis noted. Incomplete forms of this syndrome occur especially with respect to the pupil.

Several cases of this interesting condition have been studied electromyographically with the technique previously described. The innervation postulated by Bender has been confirmed in each instance.

Case 3.—A 60-year-old Negro woman developed a complete third nerve palsy due to intracranial aneurysm. A gradual recovery of lid elevation and adduction appeared six to nine months later. However, no vertical movement was elicited. On attempted gaze up or down the lid retracted and the globe was adducted. The lid also retracted on adduction and marked miosis developed. On abduction the pupil became wider. Electromyography of the levator, medial rectus, and inferior rectus revealed simultaneous discharge on attempted gaze up, down, or in (Figs. 9 and 10). A slight decrease of firing occurred in the levator on abduction.

The question arises whether anomalous innervation, as described in this paper and elsewhere,[6] plays a role in the discharge of reinnervated muscles out of their field. It does not seem likely, since the globe remains fixed and hence stretch could not occur, nor could this explain the miosis or lid retraction. On the other hand, anomalous innervation provides a new concept for this syndrome which does not require aberrant distribution of nerve fibers. At present, I feel the latter suggestion is less likely than the Bender concept but requires further consideration.

B. Progressive Nuclear Ophthalmoplegia

The etiology of this curious, often hereditary, involvement of the extraocular muscles has been long disputed. The onset is usually in early life, with ptosis and gradual weakness of all the extraocular muscles until total immobilization of the eyes results. This has been ascribed to nuclear lesions—hence the name—although, on pathological evidence, it has been maintained that the condition belongs in the category of muscle dystrophy. The following observations, the first of their kind, suggest that the disease is innervationally more closely allied to muscle pathology than to neurological pathology.

Case 4.—A 56-year-old patient had had bilateral ptosis since the age of 26. There

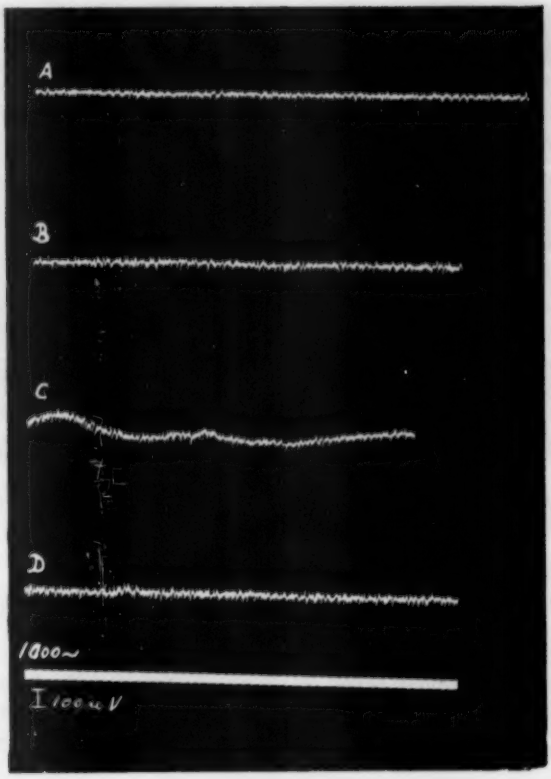


Fig. 9.—Aberrant third nerve regeneration. *A*, inferior rectus, primary position, low-amplitude discharge. *B*, Gaze down, increased discharge. *C*, Gaze in, even larger discharge. *D*, gaze up, discharge increased over initial level.

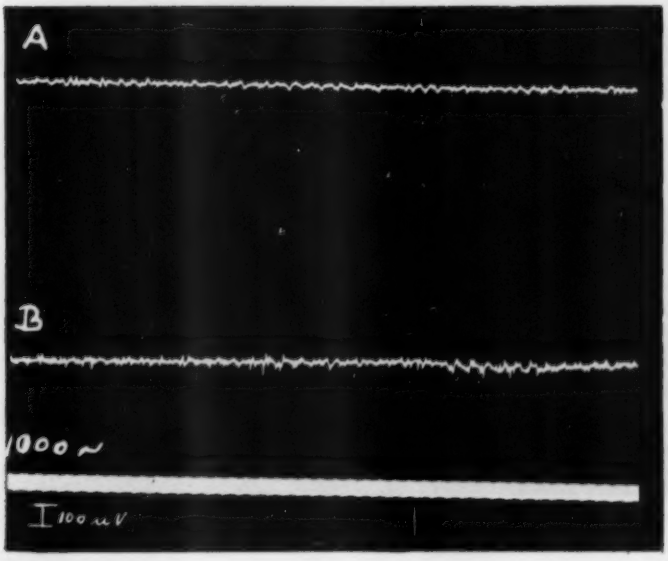


Fig. 10. — Aberrant third nerve regeneration, levator. *A*, primary position, low activity. *B*, depression of globe with increased activity in levator.

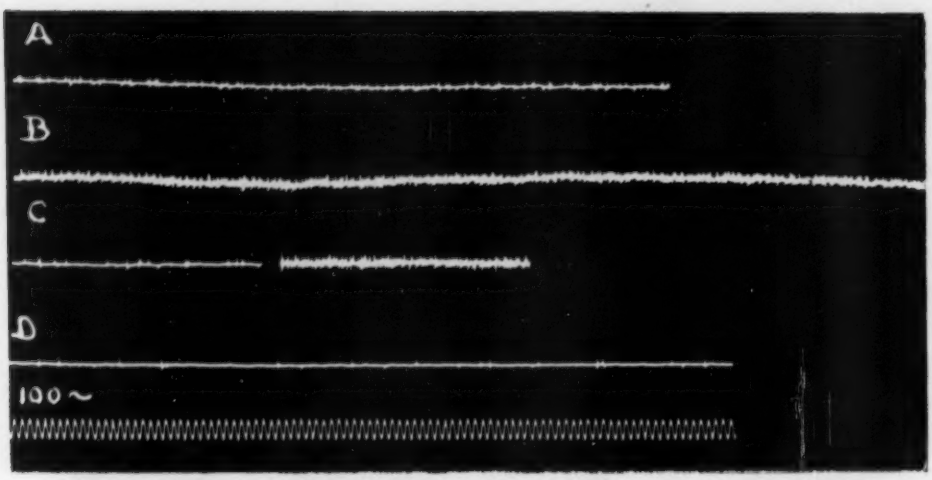


Fig. 11.—Electromyogram in progressive nuclear ophthalmoplegia (lateral rectus record). *A*, primary position. *B*, abduction, abundant recruitment but low amplitude. *C*, gaze ahead, then to side of lateral rectus. *D*, primary position, low-grade activity.

had been progressive loss of ocular motility continuing until the present. Examination revealed bilateral ptosis and almost total immobilization of both eyes. Electromyography of the lateral rectus was performed. In the primary position there was a low-frequency discharge of small motor units (Fig. 11*A*). On effort at abducting the eye there was a sustained profuse discharge (interference pattern) of very low-amplitude motor units (Fig. 11*B*). This difference is seen in Figure 11*C*, where gaze effort was directed first ahead and then to the side. No movement of the globe resulted,

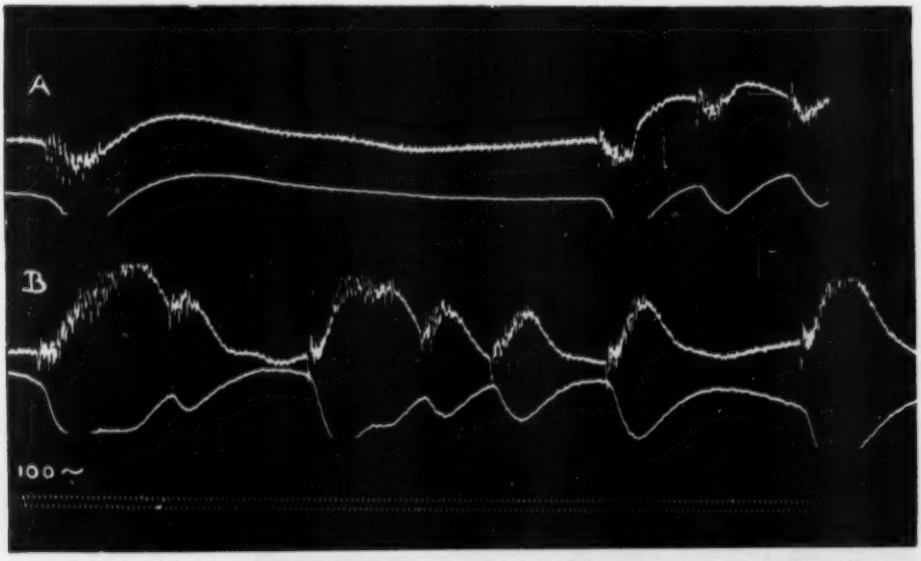


Fig. 12.—Medial rectus, progressive nuclear ophthalmoplegia. *A*, primary position. *B*, effort at adduction.

but the great increase in discharge is evident. Figure 11*D* shows single-unit activity in the primary position. Injection of neostigmine and edrophonium (Tensilon) did not alter the character of discharge.

CASE 5.—A 33-year-old woman had had bilateral ptosis since the age of 7. Gradual immobility of both eyes developed over the years, and now only a few degrees of movement are left. The EMG is identical with that of Case 4 (Fig. 12).

It has been maintained that neurogenic atrophy is characterized by the loss of complete motor units. Thus the innervational pattern on effort is a discharge of fewer motor units but with normal amplitude of those remaining. Primary muscle atrophy, however, is characterized by the loss of many muscle fibers rather than motor units.[9] Thus there is abundant recruitment of motor units on effort (interference pattern), but of lower amplitude, since the building blocks of the unit—the muscle fibers—are damaged. This is the pattern observed in the above cases. It may be objected that a neurological lesion may selectively damage large-amplitude units, leaving only small-amplitude units. The exact opposite has been noted in some neurogenic palsies of peripheral muscle. Severe neurogenic palsies of extraocular muscles usually exhibit low-amplitude potentials, but recruitment is also poor (Fig. 13). The abundant recruitment in these cases makes this seem less likely. Hence it is concluded that progressive nuclear ophthalmoplegia has close dynamic affinities with muscle dystrophy and is not primarily a neurological disorder.

C. Nystagmus

The analysis of nystagmus is substantially advanced by recording the innervation to the extraocular muscles. The pattern of discharge shows that extremely rapid frequencies may occur. The reciprocity patterns of antagonists are readily compared. The complete analysis of nystagmus involves (*a*) the innervation and (*b*) the response. The simultaneous determination of the two is obtained by recording the electro-oculogram (EOG) along with the electromyogram. The former is based on the D. C. potential of the eye and has been used for some years as an objective measure of eye movement. In Figure 14*A* and *B* the upper tracing (EMG) shows nystagmus bursts of innervation to the medial rectus. The lower tracing (EOG) records the eye movement produced. It is clear that the bursts precede the movement. The jerky type of nystagmus is indicated by the slope of the EOG. Simultaneous EMG and EOG tracings are being taken in the study of spontaneous and induced nystagmus in man.

CASE 6.—*Retractory and convergence nystagmus*

A patient with a brain tumor revealed a loss of voluntary vertical gaze associated with retractory and convergence nystagmus. Electromyograms of the medial and lateral recti revealed almost simultaneous discharge of the antagonists with resultant retraction of the globe (Figs. 15, 16). In most nystagmus the contraction of the agonist is accompanied by inhibition of the

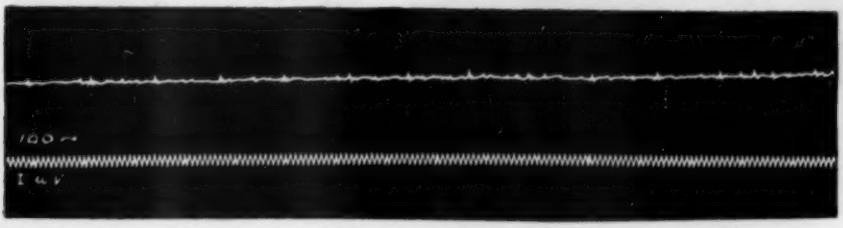


Fig. 13.—Paretic lateral rectus, attempted abduction. Low-amplitude low-frequency discharge; few units.

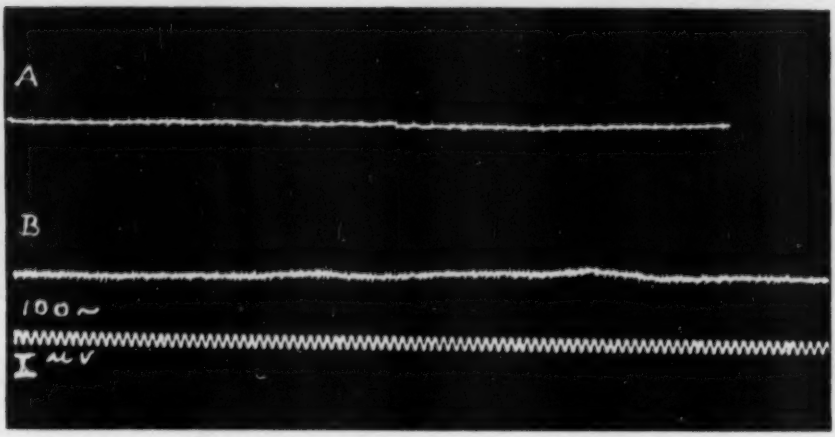


Fig. 14.—Nystagmus with simultaneous electromyogram and electro-oculogram. *A* and *B*, upper tracing, EMG of medial rectus; lower tracing, EOG. Relationship of innervation and consequent movement clearly indicated.

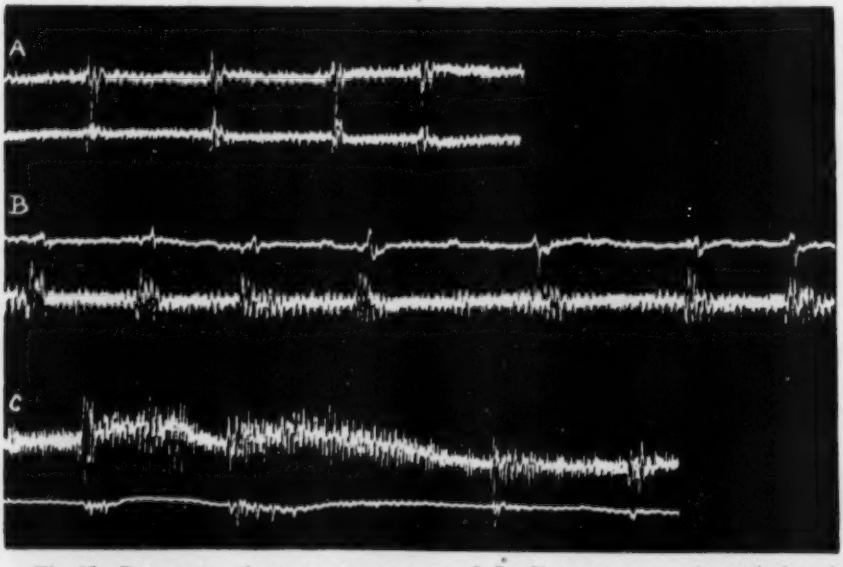


Fig. 15.—Retractory and convergence nystagmus O. D. Simultaneous recruitment in lateral rectus (above) and medial rectus (below). *A*, primary position, retractory nystagmus. *B*, convergence nystagmus. *C*, abduction with retractory nystagmus.

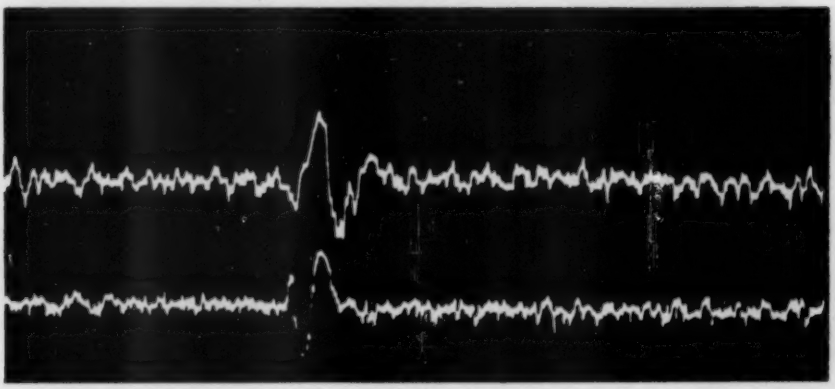


Fig. 16.—Simultaneous activity of medial and lateral recti in retractory nystagmus. Lateral rectus above. Medial rectus below.

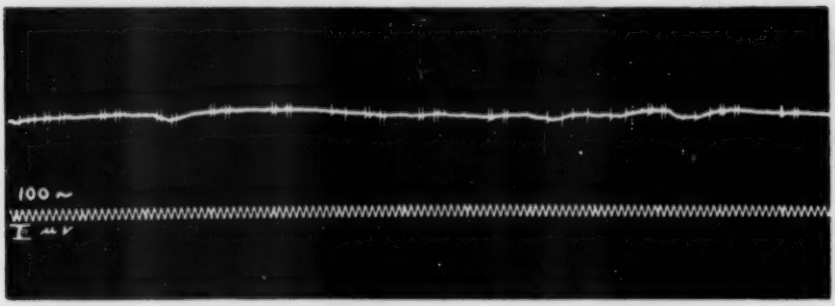


Fig. 17.—Duplex unit in lateral rectus paresis.

antagonist. This relationship was lacking during retraction nystagmus and faulty during the convergence nystagmus. A central disturbance of the reciprocity mechanism is thus evident. These two types of abnormal nystagmus appear basically similar.

550 First Ave. (16).

REFERENCES

1. Breinin, G. M., and Moldaver, J.: Electromyography of the Human Extraocular Muscles: I. Normal Kinesiology; Divergence Mechanism, A. M. A. Arch. Ophth. 54:200, 1955.

2. Breinin, G. M.: The Nature of Vergence Revealed by Electromyography, A. M. A. Arch. Ophth. 54:407, 1955.

3. Bjork, A.: Electromyographic Study of Conditions Involving Limited Mobility of the Eye Chiefly Due to Neurogenic Pareses, Brit. J. Ophth. 38:528, 1954.

4. Breinin, G. M.: The Position of Rest During Anesthesia and Sleep: Electromyographic Observations, A. M. A. Arch. Ophth. to be published.

5. Gundersen, T.: Duane Syndrome, read before the New York Academy of Medicine, Jan. 16, 1956.

6. Scobie, R. G.: The Oculorotary Muscles, Ed. 2, St. Louis, The C. V. Mosby Company, 1952, p. 262.

7. Bender, M. B., and Fulton, J. R.: Factors in Functional Recovery Following Section of the Oculomotor Nerve in Monkeys, J. Neurol. & Psychol. 2:285, 1939.

8. Breinin, G. M.: Electromyographic Evidence for Ocular Muscle Proprioception in Man, this issue, p. ???

9. Buchthal, R., and Clemmesen, S.: On the Differentiation of Muscle Atrophy by Electromyography, Acta psychiat. et neurol. 16:143, 1941.

Electromyographic Evidence for Ocular Muscle Proprioception in Man

GOODWIN M. BREININ, M.D., New York

The question of extraocular muscle proprioception* has been labored long and vehemently in ophthalmologic literature. The existence of muscle sense, that is, a knowledge of the position of the eyes due to messages from the ocular muscles, strongly advocated by Sherrington,[1] has now been generally denied. The information derived from vision and the innervational urge are said to be adequate to explain our awareness or lack of awareness of eye position.[2,3] That the extraocular muscles should lack a mechanism for the recording of muscle tension, however, would place them so far apart from other skeletal muscle as to arouse wonder and doubt that they should be so distinguished. The fact that the extraocular muscles do have anatomic and pharmacologic peculiarities has been long appreciated.

The existence of unusual nerve endings in these muscles has been reported, and the occurrence of muscle spindles and other low-threshold stretch receptors has been clearly described by Cooper, Daniel, and Whitteridge and reasons given for the failure of other workers to find them. Their recent report of recording typical stretch discharges in afferent fibers running in the third, fourth, and sixth nerves, via the fifth nerve and in the brain stem, provides clear neurophysiologic evidence for the existence of a tension-recording apparatus in extraocular muscles.[4]

It has long been known that stretch reflexes cannot be obtained from extraocular muscles. It is also realized that extraocular muscles are not extensor muscles in which phasic and static stretch reflexes are best obtained. Tendon jerk responses need not, then, be expected. That a mechanism does exist, however, for signalling changes in muscle tension is implicit in the following observations.

A. Electromyography of the extraocular muscles as described by Breinin and Moldaver[5] was carried out during enucleation procedures under local anesthesia. The level of anesthesia was sufficiently light to permit muscle movement without discomfort. The level of firing of extraocular muscle which is characteristically seen in the primary position (Fig. 1*A*) decreased radically when the muscle tendon was cut from the globe (Fig. 1*B*). Some firing continued when fascia supported the muscle and prevented complete retraction into equilibrium position. After enucleation, in another case, when the ocular muscles were maximally retracted there was no discharge in the resting rectus muscles (Fig. 2*C*). They now resembled typical peripheral skeletal muscle at rest. On attempted gaze to the side, however, they promptly fired. The only thing changed was the degree of stretch of the muscle. It is inferred, therefore, that the normal firing of the primary position is a consequence of a certain degree of tension

Received for publication June 19, 1956.

Presented before the New England Ophthalmological Society, Boston, Feb. 15, 1956.

From the Department of Ophthalmology of the New York University Post-Graduate Medical School.

Studies conducted under Grant B-911 of the National Institute of Neurological Diseases and Blindness and under grants from the National Council to Combat Blindness and the Stanley Tausend Foundation.

* Proprioception is used here in its fundamental meaning of a negative feedback mechanism controlling motor discharge, predicated on a reflex arc whose afferent end-organs are muscle spindles. Cortical awareness of position is a separate entity.

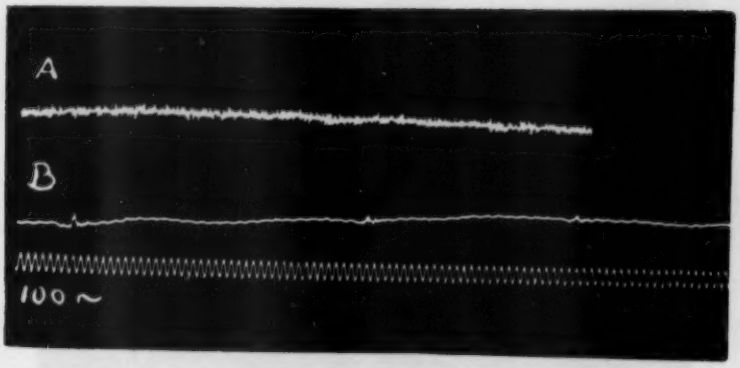


Fig. 1.—Electromyogram of a rectus muscle. *A*, before severence of tendon. *B*, after severance of tendon; note decreased activity. Amplitude of time signal, 100μv.

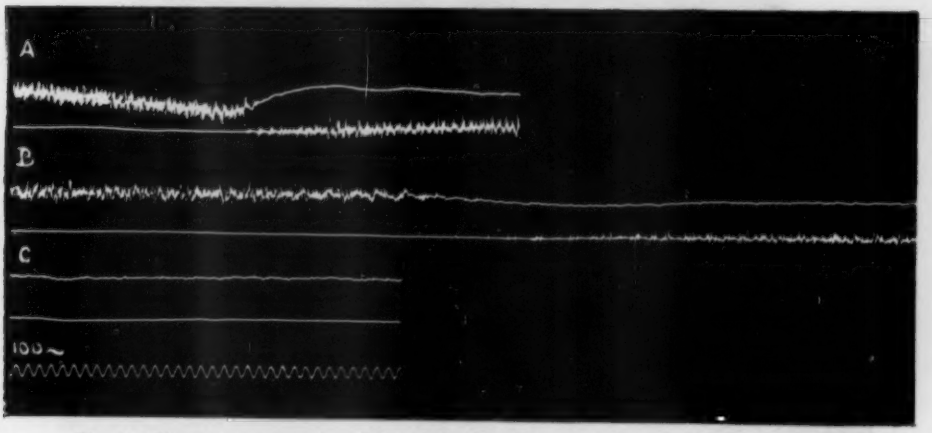


Fig. 2.—Electromyogram of medial and the lateral rectus after enucleation. *A*, reciprocal innervation rapid. *B*, reciprocal innervation slow. *C*, primary position, no activity. Amplitude of time signal, 100μv.

in the attached muscle. Retraction of the free muscle disburdens the spindle mechanism, which ceases its discharge and thus inhibits motor unit firing. The attempt to augment motor discharge above the level found just before cutting the tendon by stretching the cut muscle was unsuccessful, however. Neither was any inhibiting effect on the antagonist produced by stretching the agonist. It is clear that phasic stretch does not occur but that there is a basic, static stretch mechanism which cannot be augmented beyond some limiting point.

B. It was further observed that the reciprocity mechanism in muscles of the normal eye differs markedly from that of the enucleated eye. The beautiful reciprocal innervation of normal muscles [5] is characterized by a graded augmentation of the agonist with graded decrementation of the antagonist. On gaze from side to side the gradual increase in firing of one is accompanied by an equal decrease in firing of the other. Both fire in the primary position.

After enucleation the muscles lose this nicely graded innervation. There is abrupt increase in the agonist along with silence of the antagonist. On reversing gaze the previously active muscle quits before the new agonist commences its abrupt firing (Fig. 2*A* and *B*). It must be assumed that

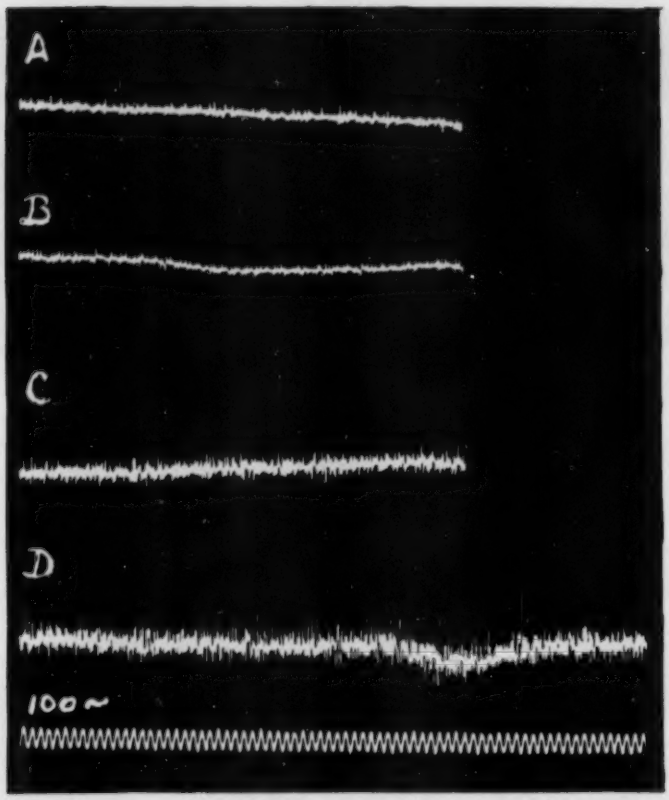


Fig. 3.—Electromyogram of paretic lateral rectus. *A*, primary position, low amplitude and frequency. *B*, abduction, low activity. *C*, adduction, anomalously increased innervation. *D*, passive adduction, even greater anomalous activity. Amplitude of time signal, 100μv.

the loss of gradation reflects the loss of an afferent mechanism in the muscles which maintains the normal level and gradation of firing.

C. A striking observation suggesting the existence of a proprioceptive mechanism has been made in seven cases of muscle paresis. Patients with third and sixth nerve palsies, in a recovering phase, have exhibited an anomalous innervation. Thus in abducens paresis the lateral rectus exhibited a small discharge in the primary position (Fig. 3*A*) and on abduction (Fig. 3*B*) but a much larger discharge on adduction, reaching its maximum as the eye rotated farthest out of the field of action of the muscle (Fig. 3*C*). This astonishing finding could not be related to electrode position and was confirmed by an increase in discharge on passive rotation of the globe with forceps out of the field of action (Fig. 3*D*). In short, the lateral rectus behaved as though it were the medial rectus. In third nerve palsy the medial rectus behaved like a lateral rectus. Recruitment occurred in the wrong field. Despite the discharge, however, the muscle could not preponderate over or even hold its own with the simultaneously firing nonparetic antagonist.

The extent to which the paretic muscle loses its identity may be seen in Figures 4 and 5. The upper tracing is the right medial rectus; the lower is the paretic right lateral rectus. This patient also was in the recovery phase of an abducens palsy. The eye could be abducted slightly but did not

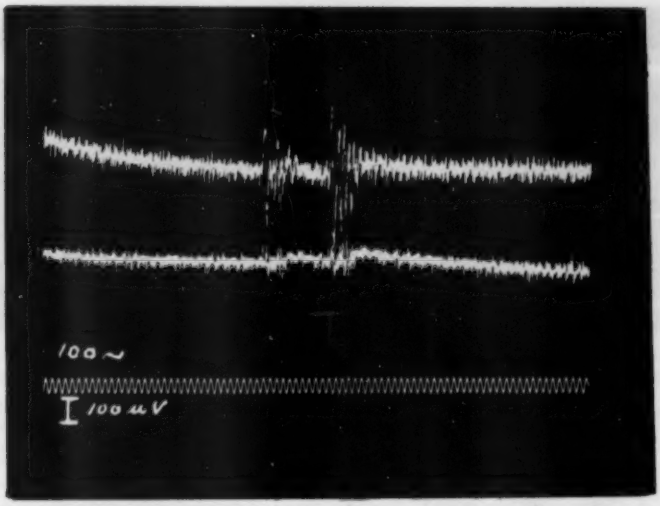


Fig. 4.—Electromyogram of right medial (above) and right lateral (below) rectus in abducens palsy O.D. Nystagmus to left, both muscles recruit together.

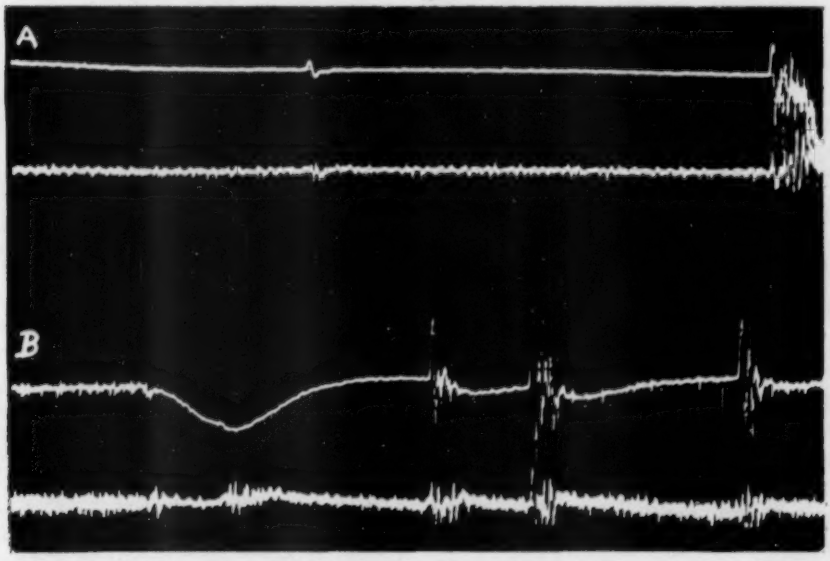


Fig. 5.—*A*, left nystagmus in dextroversion. Same case as in Figure 4. *B*, inhibition of right lateral rectus (below) on gaze right followed by increased innervation and then bursts simultaneously with medial rectus (above) in left nystagmus. Amplitude of time signal, 100μv.

quite reach the midline. The medial rectus fired huge nystagmus bursts and showed great amplitude of discharge. The innervation of the lateral rectus was surprisingly good, but, again, recruitment existed only in adduction and not in abduction. The same phenomenon occurred in passive adduction by traction. In nystagmus to the left the lateral rectus behaved like the medial —both firing large bursts in the quick phase. At times there was no accompanying discharge from the lateral rectus. In opposite

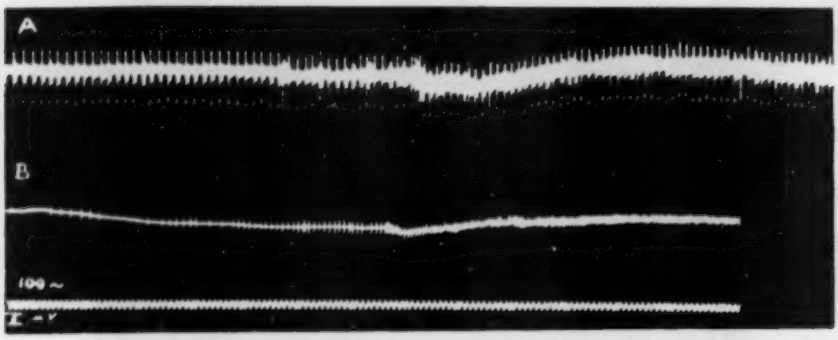


Fig. 6.—Electromyogram of paretic lateral rectus, showing anomalous innervation with single motor units on adduction by volition or traction. *A* and *B*, gaze ahead, then in.

nystagmus both exhibited inhibition at the same time or no change occurred in the lateral rectus. At no time did it augment in its proper field. A slight time lag may be noted between the initial discharge of the medial rectus and the anomalously firing lateral rectus (Figs. 4 and 5).

The only explanation I can propose for this behavior is the presence of a sensitized stretch reflex produced or made manifest by the paresis. Thus, the elongated muscle is stimulated to fire by active and passive rotation of the globe out of its field. Anomalous innervation with single motor units has been seen in a case of paretic lateral rectus. On adduction by volition and traction there occurred increased frequency and recruitment (Fig. 6). This has never been observed in a normal muscle. Why this phenomenon appears only in some paretic muscles is not presently clear.

The same phenomenon has been clearly noted in a case of Duane's syndrome.[6] In this patient, however, passive nasal rotation did not elicit a discharge from the lateral rectus. The relationship of anomalous innervation to aberrant regeneration is also discussed in that paper.

For the above reasons and in consideration of the findings of Cooper, Daniels, and Whitteridge,[4] it appears that a proprioceptive mechanism must be postulated for the extraocular muscles. It is not implied that such a mechanism provides muscle position sense or awareness. Failure to make this distinction has resulted in confusion in the past.

550 First Ave. (16).

REFERENCES

1. Sherrington C. S.: Observations on the Sensual Role of the Proprioceptive Nerve Supply of the Extrinsic Ocular Muscles, Brain 41:332, 1918.

2. Irvine, S. R., and Ludvigh, E. J.: Is Ocular Proprioceptive Sense Concerned in Vision? Arch. Ophth. 15:1037, 1936.

3. Adler, F. H.: Physiology of the Eye: Clinical Application, Ed. 2, St. Louis, The C. V. Mosby Company, 1953.

4. Cooper, S.; Daniel, P., and Whitteridge, D.: Muscle Spindles and Other Sensory Endings in the Extrinsic Eye Muscles: The Physiology and Anatomy of These Receptors and Their Connections with the Brainstem, Brain 78:564, 1955.

5. Breinin, G. M., and Moldaver, J.: Electromyography of the Human Extracular Muscles: I. Normal Kinesiology; Divergence Mechanism, A. M. A. Arch. Ophth. 54:200, 1955.

6. Breinin, G. M.: Electromyography—A Tool In Ocular and Neurologic Diagnosis: II. Muscle Palsies, this issue, p. 165.

Unilateral Headache and Oculomotor Paralysis Not Caused by Aneurysm

HARVEY A. LINCOFF, M.D. and DAVID G. COGAN, M.D., Boston

The symptom combination of unilateral frontal headache and oculomotor paralysis has long been recognized by clinicians as characteristic of aneurysm of the intracranial portion of the carotid artery. Prior to the introduction of arteriography by Egas Moniz,[1] in 1927, confirmation of the diagnosis was limited to the relatively few cases which were explored surgically or came to autopsy. With the increased use of arteriography and the increased frequency of surgical exploration in the past 15 years, faith in the symptom complex has grown to such an extent that it is now often regarded as diagnostic of intracranial carotid aneurysm.

It is aneurysms of the internal carotid artery which cause the syndrome of unilateral frontal headache and oculomotor paralysis. Only occasionally do these symptoms occur with aneurysms elsewhere. Walsh and King[2] studied a series of 32 intracranial aneurysms selected for ocular signs. Fifteen of these had aneurysm of the internal carotid artery, and, of these fifteen, fourteen presented the syndrome. In only one instance did the syndrome occur in connection with an aneurysm elsewhere (a large saccular aneurysm arising at the junction of the middle cerebral and posterior communicating arteries).

In Dandy's[3] monograph on intracranial aneurysm, published in 1944, one hundred two cases were reviewed. Fifty cases were aneurysms of the carotid artery. Of these, 23 had unilateral frontal headache and oculomotor paralysis; in 4 the headache and oculomotor paralysis were present, but the headache was not localizing; 10 had either unilateral headache or oculomotor paralysis, but not both; there were no ocular signs in the remaining 13 cases. Dandy concluded, "Perhaps the most important evidence of aneurysm is the sudden repeated sharp pains in the eye or in the frontal or temporal region, frequently followed by ptosis of the upper lid and extraocular palsies on the same side. These manifestations are almost pathognomonic of carotid or nearby aneurysms."

Jaeger[4] presented a paper in 1950 on the syndrome of frontal headache and oculomotor paralysis, in which he described 31 cases in which the clinical diagnosis was based on these two factors. In every instance the patient was proved to have an aneurysm of the intracranial portion of the carotid artery by arteriography or operative exposure.

Henderson[5] reported 119 cases of cerebral aneurysm in 1955. While he apparently agreed to the value of pain and oculomotor palsy as diagnostic and localizing symptoms in his own series, these symptoms did not occur as consistently in his cases of carotid aneurysm as in those series previously mentioned. Pain and oculomotor palsy were present in 17 cases (14%) of cerebral aneurysms of all types and in 37% of the carotid aneurysms. Three were intracavernous carotid aneurysms; twelve were supraclinoid carotid aneurysms, and two were in the posterior communicating artery. It will be noted, however, that in every instance but two the symptoms, when they occurred,

Received for publication Aug. 17, 1956.

From the Howe Laboratory of Ophthalmology, Harvard Medical School, Massachusetts Eye and Ear Infirmary. Heed Fellow from New York University Post-Graduate Medical School, New York (Dr. Lincoff).

correctly indicated an aneurysm of the intracranial portion of the carotid artery.

The foregoing clinical observations account for the prevalent belief that unilateral headache and oculomotor palsy are almost pathognomonic of aneurysm of the carotid artery involving that short stretch of the artery from the carotid canal to its division into anterior and middle cerebral vessels, i. e., its intracranial length. It is in this region that the carotid artery is so close to the third, fourth, fifth, and sixth cranial nerves that any aneurysmal expansion or rupture of the vessel is apt to present symptoms referable to the eye.

It is the purpose of this paper, on the other hand, to present and analyze a group of 12 cases with the syndrome of frontal headache and unilateral third nerve paralysis in which the etiology was found to be other than aneurysm.

Report of Cases

CASE 1.—*Diabetes*

A 57-year-old Italian-American mother of seven was admitted to the neurological service of the Massachusetts General Hospital with ptosis of the right eye, double vision, and pain over the right side of the face and head. The onset of pain had been abrupt 9 days previously, and ptosis and diplopia had followed in the next 48 hours. The only other illness the patient could recall was a right Bell's palsy five years earlier, from which she had recovered in two months. There was no history of diabetes in the family.

Examination showed a relatively complete extraocular third-nerve paralysis on the right. The fourth and sixth nerves were intact. The right pupil reacted sluggishly. There was some hypesthesia over all of the branches of the trigeminal nerve. Vision was 20/20 O. U. There was a small hemorrhage noted beside the disc in the left eye. It was said to be old and was considered a part of her recently discovered hypertension (blood pressure 170/95). The remainder of the neurological examination, including examination of the spinal fluid and electroencephalogram, was negative. A 4+ sugar was reported on routine urinalysis but was unfortunately overlooked; no blood sugar determination was made. Aneurysm of the intracranial portion of the carotid artery was considered most likely by all the hospital services. Because a bruit was heard on the left (opposite) side, it was thought that the aneurysm was in the left cavernous sinus, although all consultants were at a loss to explain the crossed signs. Skull films were normal. Arteriography was performed on the left. No aneurysm was found. In retrospect it was thought that the cavernous portion of the carotid artery was slightly narrowed and that this accounted for the bruit. Five days later right carotid arteriography was performed and again no aneurysm was found. The patient, however, developed a left hemiparesis following the procedure. When she was discharged, one month later, it was noted that the hypesthesia of the trigeminal nerve had disappeared and that the paresis of the third nerve had markedly improved. The hemiparesis remained unchanged.

The patient lived six years after the above admission. Diabetes mellitus was diagnosed two years later by her family physician. While the diabetes was moderate in degree and controlled by diet, she nevertheless developed diabetic gangrene of the toes of the right foot and extensive diabetic extravasations in the retina.

CASE 2.—*Diabetic neuropathy*

A 62-year-old housewife was admitted to the neurological service of the Massachusetts General Hospital with ptosis of the left lid and left-sided headache. Five weeks previously she had developed a left frontal headache of intermittent knife-like character, followed two days later by diplopia and four days later by drooping of the left lid. The ocular symptoms persisted and were stationary. The pain radiated to the left orbit, continued intermittently, and was accompanied by photophobia and lacrimation in the right (opposite) eye. The patient stated that she had had diabetes mellitus

for 10 years, which was in good control with 10 to 30 units of protamine zinc insulin (PZI) once a day. The medical work-up confirmed that the insulin control was good, but it disclosed evidences of diabetic complications, viz., albuminuria, casts in the urine, absent pulses in the ankles and feet, and a blood pressure of 184/102.

On ophthalmologic examination it was noted that the left lid was ptotic, the eye was rotated laterally, and there was complete external ophthalmoplegia. The pupil was normal in size and reacted to light. Corneal sensitivity was equivocal. There were diabetic changes in the retina of moderate degree. The left eye was exophthalmic by 2 mm. in comparison with the right. Except for paresthesias in the feet, the neurologic examination was negative. The spinal fluid was clear and without cells. The spinal fluid protein was 72 mg. per 100 cc. A tentative diagnosis of intracranial aneurysm, or tumor, was made.

Left carotid arteriography was performed on the fourth hospital day, and the intracranial vessels were found to be normal. The following day the patient developed laryngeal edema and died a sudden cyanotic death. Examination of the brain showed a fusiform swelling of the intracranial portion of the third nerve on the left. Histological study of the affected portion of the nerve revealed ischemic destruction and fibrous hyperplasia, largely of the central fibers. The histologic aspects of this case are being reported in a separate communication by Dreyfus, Hakim, and Adams.[6]

CASE 3.—*Diabetes*

A 74-year-old widow, born in the Azores, was admitted to the neurological service of the Massachusetts General Hospital with pain behind the right eye, ptosis of the right lid, and double vision of one week's duration. Past history disclosed that she had had uveitis in both the right and left eye, 12 and 5 years previously, respectively. She had been a diabetic for 15 years and had been hospitalized numerous times when the diabetes was out of control.

Examination showed that there was complete paralysis of all the extraocular muscles supplied by the third cranial nerve on the right. The fourth, fifth, and sixth nerves were unaffected. Pupillary response could not be evaluated because of posterior synechiae from the old uveitis. There were bilateral immature cataracts and diabetic retinopathy of moderate degree. Neurological examination, including skull films, did not contribute anything further. A primary diagnosis of diabetic neuropathy was made. Aneurysm of the intracranial portion of the carotid artery could not be ruled out, but the pain was not considered sufficiently episodic to be characteristic of aneurysm. Arteriography was not performed because of the patient's age. Two and a half months later the patient had fully recovered. Eight months later the patient developed a left oculomotor paralysis, which ran a similar course to complete recovery. A four-year follow-up disclosed the patient at age 78 living and well except for some peripheral neuropathy of the distal extremities and diabetic retinopathy which had curtailed her ability to read. Because of the multiplicity of her peripheral neuropathic signs, this case was considered to be one of diabetic etiology.*

Differential Diagnosis of Diabetes and Carotid Aneurysm.—It would be useful to be able to make a clinical differential diagnosis between aneurysm and diabetic neuropathy, because diabetics have an unusually high morbidity following arteriography (presumably owing to the fragility of the vasculature). It does not seem to be possible to make the differential diagnosis on the basis of the acute symptomatology. With both diabetic and aneurysmal ophthalmoplegia the onset is sudden and there is frequently severe pain. The pain is lateralized to the paretic side and can be episodic in nature. It is of interest that there is a prevalent clinical opinion that pain is less intense or absent in diabetic lesions. This is not borne out by our experience nor that

* Dr. Albert Weiser provided the follow-up case report on this patient.

Characteristics of Four Cases of Diabetic Neuropathy Simulating Aneurysm

Case	Age	Pain	Oculomotor Paresis	Pupil Paresis	5th Nerve Anesthesia	Retinopathy	X-Rays of Skull	Arteriogram	Other Episodes
1	57	+	+	+	+	+	−	−	7th nerve palsy 5 yr. before
2	62	+	+	?	−	+	−	−	Peripheral paresthesias
3	74	+	+	?	−	+	−	Not done	Opposite 3rd nerve paresis 8 mo. later
4*	62	+	+	−	−	+	−	−	

* Reference 7.

of Eareckson and Miller,[7] Waite and Beetham,[8] Duke-Elder,[9] and Walsh.[10]

A tabulation (Table) of the characteristics of the preceding cases, plus the well-documented case of Eareckson and Miller,[7] suggests that there are some qualities useful for differentiating diabetic neuropathy from aneurysm: All of the diabetic patients were in the fifth, sixth, or seventh decades; the youngest was 57 years old, and the average age was 64 years. In Henderson's[5] series of aneurysms, on the other hand, the highest incidence was in the 31- to 50-year-old group; less than 3% were above age 61. It is noteworthy that none of our cases occurred in juvenile diabetics. In every case diabetic retinopathy was present. Except for Case 1, diabetes had been known to be present at least seven years. Most significant, it is felt, is the presence of other neuropathy in all of the cases in the recent history or early subsequent course. All of the above cases that survived recovered complete function in less than two and a half months. The recovery following aneurysm, as Jaeger[4] points out, varies with the extent of damage. Small defects have been observed to disappear within a week. Nerves more extensively injured may not recover for as long as a year, and some 50% recover incompletely or not at all. Walsh[2] is of the opinion that aberrant regeneration is a frequent aftermath of palsies secondary to aneurysm. Aberrant regeneration has never been reported following a diabetic lesion of an oculomotor nerve. Stiff neck or blood in the spinal fluid in the presence of the aneurysm syndrome would, of course, be strong evidence against the diagnosis of diabetes. It is of interest that exophthalmos of a moderate degree does not preclude diabetes—witness the exophthalmos which contributed to the mistaken clinical diagnosis in Case 2.

In summary, it is felt that a case of diabetes which presents a classical aneurysm syndrome cannot always be differentiated from an intracranial carotid aneurysm without an arteriogram; however, given a patient of 60 years or older, with diabetic retinopathy, a negative spinal fluid, and the absence of a stiff neck, one is probably justified in postponing carotid arteriography.

CASE 4.—*Lymphatic leukemia or diabetes*

A 72-year-old farmer was admitted to the Massachusetts Eye and Ear Infirmary with pain behind the left eye and over the left forehead, double vision, and ptosis of the left upper lid. The patient gave a history of sudden onset of diplopia six weeks previously. Four weeks later he developed pain about the left eye, and ten days before admission the left lid began to droop. The patient had had diabetes for 12 years and was taking 40 units of protamine zinc insulin.

On examination it was noted that the left lid was ptotic and the left eye was deviated laterally, indicating that there was an external third nerve paralysis. Opticokinetic nystagmus was poor to the right. Visual acuity was R. 20/20, L. 20/25. The pupils were normal and fields were full. There was a small hemorrhage in the left fundus. Except for the ocular signs, the neurologic examination on the day of admission was negative. Six days later a paresis of the left sixth nerve was noted. A tentative diagnosis of aneurysm of the intracranial portion of the carotid artery was made.

X-rays of the skull and electroencephalographic studies were normal. The spinal fluid was clear, with an initial pressure of 170 mm. of water. Protein was 51 mg/100 cc; sugar, 124 mg/100 cc. There were 22 lymphocytes per cubic millimeter. The Wassermann test was negative. Because of the abnormal lymphocyte count in the spinal fluid, a complete blood study was ordered, and 28,000 WBC per cubic millimeter were found, of which 85% were lymphocytes; a diagnosis of chronic lymphatic leukemia was made. The oculomotor defects improved markedly in the next three weeks. It was concluded that the presence of lymphocytes in the spinal fluid was indicative of a leukemoid infiltration of the oculomotor nerves.

Diamond [11] has shown that in over 90% of the cases of leukemia there is some infiltration in the central nervous system. It is estimated that neurologic signs are present in 25% of these cases. An analysis of the records of 334 cases of leukemia in Boston by Schwab and Weiss [12] revealed an incidence of 20.5% of neurologic signs. The most frequently occurring signs were unilateral or bilateral palsies of the 7th and 6th nerves, with less frequent involvement of the 5th, 8th, 9th, 10th, 11th, and 12th nerves. The spinal fluid was abnormal in 75% of cases, showing increased cell count, increased protein, and decreased sugar.

The cranial nerve palsy in Case 4 cannot positively be said to result from leukemic infiltration. The features of the case fit the criteria for a diabetic neuropathy as well.

CASE 5.—*Meningioma*

A 65-year-old widow was referred to the neurologic service of the Massachusetts General Hospital with a diagnosis of intracranial aneurysm. Her left lid was ptotic, the left eye was relatively immobile, and the patient complained of having had intermittent left frontal headache and diplopia four years previously, which had been diagnosed as a "stroke." The diplopia had persisted, and the headache had recurred intermittently. One and a half years before admission the left lid began to droop; this condition had progressed until on admission the left eye was nearly closed.

Examination showed complete paralysis of the third and sixth nerves, partial paralysis of the fourth nerve, and partial involvement of all branches of the fifth nerve. There was an exophthalmos of 3 mm. of the left eye, which was attributed to weakness of the extraocular muscles. Visual acuity was R. 20/30, L. 20/70. The fields were normal. The fundi showed Grade I hypertensive changes consistent with a blood pressure of 190/110. Except for the cranial nerve defects, the neurological examination was negative. A spinal tap showed an initial pressure of 170 mm. of water. The fluid was clear, colorless, and contained 2 WBC. The protein was 28 mg/100 cc. Skull films showed generalized osteoporosis of the calvarium and sella turcica. An electroencephalogram was read as normal. A tentative diagnosis of aneurysm of the intracranial portion of the carotid artery was agreed upon, and arteriography was performed. No aneurysm was found. The internal carotid artery was noted to be displaced medially and upward. It is interesting that at this point a senior consultant pointed out that in a recent publication by Alpers and Ryan [13] two cases of aneurysm had been presented "with this classical syndrome" which, in spite of negative arteriograms, proved upon exploration to be aneurysms. Special views of the sphenoid were obtained, which showed definitely increased density of the greater wing of the sphenoid. On review of the original films, the sphenoid density was verified. This information, together with the displacement of the carotid siphon, was regarded as diagnostic of a meningioma. In view of the patient's age and hypertension, removal of the tumor was deferred. The patient died five months later in "cardiac failure." No autopsy was obtained. The patient's eye symptoms were unchanged prior to death.

CASE 6.—*Glioblastoma*

A 42-year-old truck driver was admitted to the neurosurgical service of the Massachusetts General Hospital with a diagnosis

from the referring physician of subarachnoid hemorrhage. The patient had been well until three weeks previously, when he had had a sudden onset of severe pain in the left eye and left frontal region, followed by drowsiness and intermittent unconsciousness. His condition had improved but his headache recurred intermittently, and so he was admitted to an outside hospital. A lumbar puncture was performed and showed xanthrochromic fluid under normal pressure. Left carotid arteriography did not reveal any abnormality. The patient was referred to the Massachusetts General Hospital for additional study.

Examination showed minimum ptosis (the left lid was 2 mm. lower than the right) and diplopia indicative of paresis of those recti supplied by the left third nerve. The lateral rectus and superior oblique were unaffected. The left pupil was 2 mm. larger than the right and sluggish. Accommodation was diminished on the left. Vision was R. 20/20, L. 20/20. Fields were full. The ocular fundi were not remarkable. The spinal fluid was bloody (83,000 RBC per cubic millimeter); the initial pressure was 165 mm. of water; the total protein, 340 mg/100 cc. The remainder of the neurological examination was negative. Because of the classical history and symptomatology, and in the face of a negative arteriogram from the referring hospital, the neuro-ophthalmological consultant made a tentative diagnosis of "aneurysm with rupture at the bifurcation of the left internal carotid artery." The neurological consultant suggested a thrombosis of a small pontine vessel. Additional skull films revealed thickening of the sphenoid ridge and destruction of the medial aspect of the lesser wing of the sphenoid on the right. Review of the plates from the previously performed arteriography showed anterior and upward displacement of the middle cerebral artery. An EEG suggested a tumor focus in the left frontal region. A third diagnosis of meningioma of the sphenoid ridge was added. An exploratory operation was performed and revealed a large glioblastoma multiforme coming from the anterior inferior tip of the temporal lobe. The tumor had invaded the floor of the middle fossa and displaced the brain stem. Several membranes suggestive of hematomas were encountered.

CASE 7.—*Unidentified tumor*

A 55-year-old man entered the Massachusetts General Hospital with ptosis of the left upper lid. One year previously he had suffered headache and ophthalmoplegia of the left eye, from which he had recovered. Six months before admission, limitation of motion was again observed in the left eye. The extraocular paresis grew progressively worse. Two weeks before admission the left lid drooped. At this time the diagnosis of aneurysm of the intracranial portion of the carotid artery was made and the patient was referred to the Massachusetts General Hospital for treatment. On examination, the external portions of the eye, apart from the muscles, were normal. Vision was R. 20/30, L. 20/50. The fundus was not remarkable. X-rays of the skull were initially read as negative. Review of the films, however, showed destruction of the right clinoid process and superior aspect of the clivus. The diagnosis was changed to probable intracranial neoplasm, although aneurysm could not be ruled out. No treatment was undertaken at that time. Four months later the patient showed beginning involvement of the left fifth nerve. In another four months, x-rays showed destruction of the pituitary fossa and complete loss of the dorsum sellae and posterior clinoids. The following month a central scotoma was picked up in the left eye, and in the next four months vision was rapidly lost in this eye and optic atrophy appeared. One year later an upper temporal defect appeared in the right visual field. At this time an exploratory operation was performed, and a tumor was found at the base of the brain adjacent to the sella. Because of much bleeding no biopsy was attempted. The patient died postoperatively.

Differential Diagnosis of Tumors.—In the three cases of tumor just presented, it

is of interest that a correct diagnosis was available from the x-ray films in every case but was not believed in view of the aneurysm-like symptoms. Displacement of the carotid siphon is usually present with a tumor simulating aneurysm and occurred in both of our cases in which arteriography was performed. The EEG was positive in only one case; however, in this instance it was localizing. Except in the presence of intercurrent subarachnoid hemorrhage, the symptoms tend to be progressive. None of our cases showed papilledema, and it would not be expected, because the lesion is not in an area in which it would early interfere with spinal fluid dynamics. (Papilledema with or without retinal hemorrhage is variously reported as being in 11% to 40% of aneurysms that bleed).

CASE 8.—*Ophthalmoplegic "migraine"*

An 11½-year-old girl was admitted to the neurologic service at the Massachusetts General Hospital with left orbital pain, ptosis, and diplopia. Eleven days previously she had awakened with severe pain deep in the left orbit and was unable to open the left eye. When the lid was raised she saw double. The pain had diminished prior to admission, but the paretic symptoms remained unchanged. The past history revealed that since the age of 2 years the child had had periodic pain lasting 3 to 48 hours, behind the left eye, associated with nausea and vomiting. These attacks had been decreasing in frequency as she grew older, but they had occurred eight times in the preceding two years. There had never been any paretic symptoms accompanying the attacks prior to the episode for which she was admitted.

On admission, examination revealed the presence of a complete external and partial internal third nerve paralysis. The left pupil was mid-dilated and reacted sluggishly. The other cranial nerves were normal, and the remainder of the neurological examination was mid-dilated and reacted sluggishly. The was 166 mm. of water. There were 28 RBC per cubic millimeter in the spinal fluid, but no xanthrochromia; the cells were ascribed to trauma resulting from the puncture. A complete medical study was essentially negative. Skull films were normal. A presumptive diagnosis of aneurysm of the internal carotid artery was made, and an arteriogram was performed. No abnormality of the vessels was found. The arteriogram was thought to be of good quality and to rule out aneurysm; moreover, 11½ years was considered an early age, although not unique,[3,5,14] for a congenital aneurysm to manifest itself. It was concluded that the case was either idiopathic ophthalmoplegia, of a type with a favorable prognosis seen in children, or ophthalmoplegic migraine.

A month later the child had completely recovered.

CASE 9.—*Ophthalmoplegic "migraine"*

A 4½-year-old girl was seen as an outpatient with right-sided ptosis and paresis of those ocular muscles supplied by the third nerve. Ten days previously she had developed a headache over the right eye and had vomited, after which the right lid was noted to droop. This did not cause any great alarm initially, because it was the third occasion since the age of 2 years that the child had experienced this syndrome and in each instance the symptoms had resolved spontaneously within five days without complications. On this occasion, however, the symptoms persisted and consultation was sought.

Examination showed a relatively complete third nerve paresis, with a dilated pupil which reacted poorly to light. There were no other significant neurological defects. It was noted that the mother had had migraine headache but never any ophthalmoplegia. A presumptive diagnosis of aneurysm of the internal carotid artery was made. The child was observed over the next month, and function was noted to improve steadily. Nevertheless, because of the typical aneurysm-like quality of the symptoms and their recurrent nature, right carotid arteriography was performed; the cerebral vascular system was found to be normal. While the child was under anesthesia spinal fluid was

withdrawn, and this was also found to be normal.

In view of the negative studies a diagnosis was made of ophthalmoplegic migraine (cyclic oculomotor paralysis). A five-year follow-up revealed that the child continued to have similar episodes one to two times a year. They have become less severe as she grows older; the oculomotor paresis, particularly, is diminishing in severity. It has been noted that the attacks tend to occur in August around her father's birthday.

Comment.—Ophthalmoplegic migraine is a rare entity, and, because it is a descriptive diagnosis and not an etiological one, the diagnosis should be made with caution. Dandy [3] described cases which were diagnosed as migraine but which eventually bled intracranially and on exposure at surgery or autopsy were shown to be aneurysms.

Nevertheless, the combination of recurrent nausea and vomiting, lateralizing pain, and ophthalmoplegia is recognized in young persons as a syndrome which spontaneously remits as the child grows older. This is variously called ophthlamoplegic migraine or cyclic oculomotor paralysis. Walsh [10] regarded ophthalmoplegic migraine as a clinical entity characterized by periodicity of symptoms beginning in youth. The paresis lasts from a few hours to weeks or months and may be permanent. The third nerve is by far the most frequently involved. Walsh made a special point of the fact that the pupil is nearly always involved, as it was in both of our patients. He reported a case in a 13-year-old boy in whom the symptoms began at 3 years of age. In all respects it was similar to Case 9 above.

Harlowe [15] reported a case of ophthalmoplegic migraine in a 45-year-old woman who had had migraine-like headaches for eight years coincident with her menses. She had had periodic urticaria since the age of 17. On one occasion she developed a unilateral third nerve paresis with pupillary involvement following a typical attack of migraine. Recovery occurred in four weeks.

The following case from the literature, by R. V. Coxon,[16] is described in some detail because it is a typical aneurysm-like syndrome, but of a source which we have not encountered, namely, hemorrhage into a pituitary tumor.

A 29-year-old man was seized with sudden severe headache referred to both temporal regions. Shortly thereafter he developed diplopia. The symptoms persisted over the next two days, and he became progressively drowsy. He was admitted to Guy's Hospital, and a spinal tap showed a protein of 170 mg/100 cc., 5 RBC, 28 lymphocytes, and 8 polymorphonuclear leukocytes. No bacteria were found. Two days later a left ptosis appeared and examination revealed a complete external left third nerve paralysis. The patient improved markedly in the next three weeks. Although x-rays of the skull showed enlargement of the sella turcica, a diagnosis of aneurysm of the intracranial portion of the carotid artery was favored. For this reason a left carotid arteriogram was performed. No aneurysm was found. During the night following the procedure the patient developed respiratory embarrassment, and, though a large amount of blood clot was evacuated from the neck, he died. Autopsy revealed a walnut-sized tumor beneath the diaphragm of the sella, with evidence of a large hemorrhage in its substance.

It was recalled that the patient's lower jaw had been noted to be large and the teeth widely spaced, but these features had been regarded as within normal limits.

Pituitary adenoma without hemorrhage, but nevertheless simulating aneurysm of the carotid artery, has been discussed by Weinberger, Adler, and Grant [17] in a report of 14 cases. In six of their patients symptoms referable to the ocular and trigeminal nerves comprised the entire neurologic picture; in the remaining eight cases, while the symptoms were present, visual field defects were also present.

Summary

Although the syndrome of unilateral frontal headache and oculomotor paralysis

is oftenest associated with intracranial saccular aneurysm, especially when of abrupt onset, the syndrome may occur with other types of lesions. In the present paper three such cases are reported as due to diabetes, three due to paraclinoid tumor, one to leukemia, and two to the entity called ophthalmoplegic migraine.

Some of the aids in differentiating the nonaneurysmal entity from the aneurysmal are as follows: The diabetic cases represented an older age group and showed other evidence of diabetes. The tumor cases gave x-ray signs of erosion or extosis of the base of the skull and elevation of the carotid siphon. The leukemic patient showed lymphocytosis in the spinal fluid and other evidence of leukemia. The two patients with migraine gave a history of cyclical recurrence of the syndrome with quick and full recovery. Meningismus was absent in all.

243 Charles St., Boston 14.

REFERENCES

1. Egas Moniz: L'Encéphalographie artérielle: Son importance dans la localisation des tumeurs cérébrales, Rev. neurol. 2:72-90, 1927.

2. Walsh, F. B., and King, A. B.: Ocular Signs of Intracranial Saccular Aneurysms: Experimental Work on Collateral Circulation Through Ophthalmic Artery, Arch. Ophth. 27:1-33, 1942.

3. Dandy, W. E.: Intracranial Aneurysms, Ithaca, N. Y., Comstock Publishing Co., Inc., 1944.

4. Jaeger, R.: Aneurysm of the Intracranial Carotid Artery: Syndrome of Frontal Headache with Oculomotor Nerve Paralysis, J. A. M. A. 142:304-310, 1950.

5. Henderson, J. W.: Intracranial Arterial Aneurysms, Tr. Am. Ophth. Soc. 53:349-462, 1955.

6. Dreyfus, P.; Hakim, S., and Adams, R.: Diabetic Ophthalmoplegia, Tr. Am. Neurol. Soc., to be published.

7. Eareckson, V. O., and Miller, J. M.: Third-Nerve Palsy with Sparing of Pupil in Diabetes Mellitus: A Subsequent Identical Lesion of the Opposite Eye, A. M. A. Arch. Ophth. 47:607-610, 1952.

8. Waite, J. H., and Beetham, W. P.: The Visual Mechanism in Diabetes Mellitus (A Comparative Study of 2002 Diabetics and 457 Non-Diabetics for Control), New England J. Med. 212:429-443, 1935.

9. Duke-Elder, S.: Text-Book of Ophthalmology, St. Louis, The C. V. Mosby Company, 1954, Vol. 4, p. 4114.

10. Walsh, F. B.: Clinical Neuro-Ophthalmology, Baltimore, Williams & Wilkins Company, 1947, p. 837.

11. Diamond, I. B.: Leukemic Changes in the Brain: A Report of 14 Cases, Arch. Neurol. & Psychiat. 32:118-142, 1934.

12. Schwab, R., and Weiss, S.: The Neurologic Aspect of Leukemia, Am. J. M. Sc. 189:766-778, 1935.

13. Alpers, B. J., and Ryan, J. J.: Aneurysm of the Internal Carotid Artery with Normal Arteriogram: Report of 2 Cases, Arch. Neurol. & Psychiat. 62:520-522, 1949.

14. Hermann, K., and MacGregor, A. R.: Cerebral Haemorrhage from Rupture of Congenital Intracerebral Aneurysm in a Child, Brit. M. J. 1:523-525, 1940.

15. Harlowe, H. D.: Ophthalmoplegic Migraine: Report of a Case, Arch. Ophth. 26:1058-1062, 1941.

16. Coxon, R. V.: A Case of Haemorrhage into a Pituitary Tumor Simulating Rupture of an Intracranial Aneurysm, Guy's Hosp. Rep. 22:89-93, 1943.

17. Weinberger, L. M.; Adler, F. H., and Grant, F. C.: Primary Pituitary Adenoma and the Syndrome of the Cavernous Sinus: A Clinical and Anatomic Study, Arch. Ophth. 24:1197-1236, 1940.

Heparin in Senile Macular Degeneration

Preliminary Report

SOL ROME, M.D., Los Angeles

Recent investigations indicate that one of the major factors in the development of atherosclerosis is the state of the circulating blood lipids, or, more precisely, of the blood lipoproteins.[1,2] Heparin apparently plays a major role in the degradation or interconversion of lipoproteins from larger to smaller molecules, during their serum transport phase.[3,4] It has been postulated that endogenous heparin may be involved in a homeostatic mechanism controlling the serum transport phase of fat metabolism, similarly as insulin does in carbohydrate metabolism.[5,6] Because of its fat-clearing, or lipemia-clearing, action heparin is being used as an antiatherogenic agent; this represents a new approach to the therapy of atherosclerosis. Engelberg[7] has suggested that heparin might be of value in the treatment of eye conditions associated with arteriosclerosis. Maumenee[8] reviewed some of the present concepts of the pathogenesis of atherosclerosis and concluded: "One encouraging lead has emerged from the pharmacological treatment of arteriosclerosis [with injections of heparin]. There was great individual variation in the lipoprotein response to treatment, but in all cases there was an alteration in the serum in the direction of normality. The latter clue should be of particular significance for ophthalmologists who are interested in the treatment of senile macular degeneration."

Exclusive of articles dealing with its anticoagulant action, which is not considered in this presentation, the following publications dealing with heparin were found in the ophthalmologic literature. Bick and Wood[9] established that heparin administered to sensitized rabbits prior to the injection of antigen protected the animals against uveitis, and in another study[10] they demonstrated that heparin, given systemically, had a marked inhibitory effect on experimentally produced uveitis. Vannas[11] reported that local heparin treatment relieved pain in acute iritis and promoted resorption of recent posterior synechiae; in primary glaucoma intraocular tension was sometimes slightly reduced and heparin also seemed to contribute to the disappearance of fresh cataract masses. Vannas[12] also treated five cases of arteriosclerotic retinopathy with 50 to 100 mg. heparin daily, for periods of one to two weeks, in order to retard further progress of the disease; two cases showed certain improvement and a third one showed a still more pronounced effect, but on the whole the results are described as "not fully convincing." Berlin[13] used heparin in the treatment of diabetic retinopathy, on the theory that early arteriosclerotic signs are connected with changes in lipid metabolism; after initial trials with an intravenous dose of 25 to 30 mg. every other day, medication was increased to 50 mg. daily, for four to six weeks, and in some cases it was continued another few weeks; whenever response had been positive, a second course was given after an interval of two to three months, to control further impairment. Of a total of 30 cases, only 6 showed "rather convincing improvement," which in two instances is described as "remarkable"; in two additional cases macular changes disappeared. In the discussion of this paper, Vannas suggested that heparin

Received for publication June 11, 1956.

Presented before the Section of Ophthalmology of the Los Angeles County Medical Association, May 3, 1956.

TABLE 1.—*Summary of Cases of Senile Macular Degeneration Treated with Intravenous Heparin*

Case	Sex	Age	Heparin Therapy		Injections, No.	Vision		Pathologic Changes in the Macular Region		Assoc. Findings	Results
			Begun	Concl.		Before	After	O.D.	O.S.		
1	M	50	3/52	9/55	120	O.D. 20/70, O.S. 20/100—1	O.D. 20/25+2 O. S. 20/25—3	Disciform macular degeneration with marked colloid macular degeneration	Same	None	Markedly improved
2	M	65	1/54	7/55	50	O.D. 20/80—1, O.S. hand movements	O.D. 20/50+1, O.S. hand movements	Occlusion of superior temporal branch of central retinal artery with disciform macular degeneration	Marked arteriosclerotic and pigmentary macular degeneration	Hypertension	Moderately improved
3	F	74	6/54	12/55	90	O.D. 20/50, O.S. 20/400	O.D. 20/200, O.S. 20/400	Senile arteriosclerotic macular degeneration	Circinate retinopathy with far-advanced disciform macular degeneration	None	Worse
4	F	74	8/54	12/55	70	O.D. 20/400, O.S. 20/50	O.D. 20/400, O.S. 20/30—3	Marked arteriosclerotic senile macular degeneration with pigmentary changes; colloid degeneration	Arteriosclerotic senile macular degeneration; colloid macular degeneration	None	Markedly improved
5	M	53	9/54	3/55	60	O.D. 20/50, O.S. 20/200	O.D. 20/25—2, O.S. 20/200	Disciform macular degeneration; deep hemorrhage beneath macular region; choroidal atrophy	Marked central choriodal and retinal atrophy	None	Markedly improved
6	M	65	1/55	4/55	15	O.D. 20/200, O.S. 20/400	O.D. 20/400, O.S. 20/400	Disciform macular degeneration with circinate retinopathy; pigmentary degeneration	Old thrombosis of central retinal vein	None	Worse
7	F	77	1/55	11/55	45	O.D. 20/100, O.S. 20/400	O.D. 20/60—1, O.S. 20/400	Disciform macular degeneration with circinate retinopathy	Old disciform macular degeneration with cystoid degeneration	None	Moderately improved
8	M	69	3/55	5/55	15	O.D. 20/100, O.S. 20/40	O.D. 20/25, O.S. 20/40	Occlusion of inferior temporal artery with early disciform macular degeneration	Mild senile arteriosclerotic macular degeneration	Hypertension	Markedly improved
9	M	57	3/55	7/55	35	O.D. 20/200, O.S. 20/200	O.D. 20/200, O.S. 20/25	Immature cataract; gross fundus details	Early disciform macular degeneration with small hemorrhages	Aphakia O.S., cataract extr. O.S. 12/54	Markedly improved
10	F	67	5/55	12/55	30	O.D. 20/200, O.S. 20/400	O.D. 20/200, O.S. 20/400	Central choroidal atrophy; cholesterin crystals; colloid degeneration	Old disciform macular degeneration with large hemorrhages; circinate retinopathy	None	Stationary
11	M	79	6/55	12/55	30	O.D. 20/200, O.S. 20/60—3	O.D. 20/200, O.S. 20/30—3	Immature cataract; early disciform changes; evanescent circinate exudates	Colloid macular degeneration; early disciform changes with occasional small hemorrhages	Aphakia O.S., cataract extr. O.S. 9/54	Markedly improved

TABLE 1.—*Summary of Cases of Senile Macular Degeneration Treated with Intravenous Heparin*—Continued

Case	Sex	Age	Heparin Therapy		Injections, No.	Vision		Pathologic Changes in the Macular Region		Assoc. Findings	Results
			Begun	Concl.		Before	After	O.D.	O.S.		
12	F	75	6/55	9/55	20	O.D. 20/200, O.S. 20/70+1	O.D. 20/200, O.S. 20/40—3	Immature cataract; gross details only	Early disciform macular degeneration; diffuse colloid macular degeneration	Cataract O.D.	Moderately improved
13	M	75	7/55	12/55	10	O.D. 20/70+1, O.S. 20/60+2	O.D. 20/60, O.S. 20/60+2	Arteriosclerotic macular degeneration; diffuse colloid macular degeneration; pigmentary changes	Same	None	Slightly improved
14	F	63	7/55	9/55	10	O.D. 20/400, O.S. 20/60	O.D. 20/400, O.S. 20/400	Mature cataract	Disciform macular degeneration with atrophic pigmentary changes	None	Worse
15	F	60	7/55	2/56	30	O.D. 20/300, O.S. 20/50	O.D. 20/100, O.S. 20/50+2	Disciform macular degeneration	Central choroidal sclerosis with arteriosclerotic macular degeneration	High myopia bilaterally; hypertension	Slightly improved
16	F	61	11/55	1/56	15	O.D. 20/400, O.S. 20/30	O.D. 20/400, O.S. 20/25	Large disciform macular degeneration with large hemorrhages	Early arteriosclerotic macular degeneration; diffuse colloid macular degeneration	None	Slightly improved
17	M	68	12/55	1/56	20	O.D. 20/60+2, O.S. 20/300	O.D. 20/25+2, O.S. 20/300	Disciform macular degeneration	Normal	Amblyopia ex anopsia O.S.	Markedly improved
18	F	77	1/56	3/56	20	O.D. 20/400, O.S. 20/100	O.D. 20/200, O.S. 20/70	Central choroidal arteriosclerosis; small remaining central retinal island	Arteriosclerotic macular degeneration	None	Slightly improved
19	F	67	1/56	3/56	25	O.D. 20/200, O.S. 20/200	O.D. 20/50+, O.S. 20/40	Arteriosclerotic macular degeneration	Same	Diabetes; aphakia bilaterally	Markedly improved
20	F	61	1/56	5/56	25	O.D. blind, O.S. 20/400	O.D. blind, O.S. 20/25+1	Primary optic atrophy	Cystoid macular degeneration	None	Markedly improved
21	F	69	1/56	3/56	20	O.D. 20/400, O.S. 20/40	O.D. 20/400, O.S. 20/40—1	Arteriosclerotic senile macular degeneration	Early senile arteriosclerotic macular degeneration	None	Stationary
22	M	85	2/56	3/56	10	O.D. 20/70, O.S. 20/100	O.D. 20/70, O.S. 20/50+3	Immature cataract; early arteriosclerotic macular degeneration	Senile arteriocslerotic macular degeneration	None	Moderately improved
23	F	64	2/56	3/56	10	O.D. 20/30, O.S. 20/400	O.D. 20/30, O.S. 20/400	Beginning circinate retinopathy; early arteriosclerotic macular degeneration	Old disciform macular degeneration	Hypertension	Stationary

may be effective in diabetic retinopathy but not in arteriosclerosis; it was also stressed that in order to verify the effect of heparin a relatively large portion of the fundus should be studied in successive photographs. Mylius and Stark[14] found an increase of β-lipoproteins in a series of patients with senile macular degeneration. A preparation of heparin for intravenous injection (Thrombophob), in doses of 100 mg. daily, was used for an average period of one month in 11 cases, 5 of which are listed as improved.

Present Study

In March, 1952, a study was begun to evaluate the effect of heparin on senile macular degeneration. The series consisted mainly of advanced cases in a routine office practice. Many of the patients had already lost the central vision in one eye, and in the other the vision had declined to 20/50 or less. In a large percentage of this group previous treatment with vasodilators, iodides, and other lipotropic factors, such as Methischol * or sorethytan (20) monooleate (Sorlate) was without effect on the progressive loss of vision. The pertinent data of the 23 cases in this study are presented in chronological order, in Table 1.

Method

The dosage schedule arbitrarily used in this study was 100 mg. of the sodium salt of concentrated aqueous heparin (Lipo-Hepin, Darwin Laboratories) intravenously, twice weekly.† A series of 10 to 20 injections was given, followed by a two- to three-week rest interval. A few cases received 200 mg., subcutaneously in the fat tissue above the iliac crest, but since no better results were obtained, use of the lower intravenous dose was resumed. Clotting time determinations were omitted because the anticoagulant effect of this dose of intravenous heparin is known to be limited to less than 12 hours. The patients were cautioned to avoid bruising or cutting themselves, for instance in shaving, on the day of injection and were warned not to have minor surgical procedures scheduled on that day. All subjects, including those with advanced cardiovascular disease with or without hypertension, tolerated the treatment very well. The only contraindications to heparin therapy are active internal ulceration, chronic liver disease, and a hemorrhagic diathesis.

No untoward reactions were noted in more than 1000 intravenous injections of heparin. Two patients complained of becoming very "jittery," and one of them refused further treatment because of this unpleasant sensation (Case 2). These observations are in accord with the common experience that intravenous heparin is the safest of all anticoagulants. Nevertheless, an ampule of protamine was kept handy for intravenous administration as a heparin antagonist, but in this series no occasion arose for its use. The absence of untoward side-effects may be partially attributed to the selection of colorless concentrated (200 mg/cc.) aqueous heparin; the reprocessing

TABLE 2.—*Results of Intravenous Heparin in Senile Macular Degeneration*

Results*	Cases, No.
Markedly improved	9
Moderately improved	4
Slightly improved	4
Stationary	3
Worse	3
Total	23

*Grading of improvement: I. Markedly improved—final visual acuity 20/40 or better. II. Moderately improved—final V.A. 20/70-20/40 and an improvement of at least one line. III. Slightly improved—final V.A. less than 20/70 or an improvement of less than one line. IV. Stationary—no improvement, but no decrease of vision. V. Worse—V.A. became worse during therapy.

TABLE 3.—*Response of Various Types of Senile Macular Degeneration to Intravenous Heparin*

Predominant Macular Lesion	Marked Improvement	Moderate Improvement	Slight Improvement	Stationary	Worse
Disciform (12 cases)	6	3	1	0	2
Arteriosclerotic (10 cases)	2	1	3	3	1
Cystoid (1 case)	1				

* A preparation containing choline chloride, DL-methionine, inositol, vitamin B_{12}, and liver concentrate.

† Some of the heparin used in this study was donated by Darwin Laboratories, Los Angeles.

necessary for this concentration results in a more highly refined product.[15]

Results

Table 2 presents a summary of the results arbitrarily graded into five groups, on the basis of corrected visual acuity.

In Table 3 the results of treatment are broken down in accordance with the predominant type of macular involvement. In this series of cases marked improvement was much more frequently obtained in the disciform type of macular degeneration.

Several illustrative cases are presented.

Report of Cases

CASE 1.—A 50-year-old male truck driver was first seen in July, 1950; vision was 20/30, corrected, both eyes. External eye examination was negative; media were clear; discs were normal. There was diffuse colloid degeneration (Tay's guttate central choroiditis) of both posterior polar areas, with very early disciform changes. Despite treatment with various vasodilators, iodides, and Methischol, the vision gradually diminished. One year later, in June, 1951, visual acuity was O. D. 20/50, O. S. 20/70. Fundus photographs at that time (Figs. 1A and 1B) show the colloid macular degeneration, the disciform involvement, and the beginning pigmentary changes in both macular areas. After another eight months, in February, 1952, immediately before the start of heparin therapy, vision had further declined to O. D. 20/70, O. S. 20/100−1. The disciform swelling of the macular regions had increased, and the pigmentary changes in both fundi were more marked (Figs. 1C and 1D). Heparin was administered intravenously, at first 100 mg. every fifth day, for a total of five injections, after which the vision was O. D. 20/50, O. S. 20/70; no change could be seen in the fundus picture. Since there were no untoward side-effects, it was decided to modify the schedule and give two injections weekly. After three months of heparin therapy, vision was O. D. 20/40, O. S. 20/50; there was still no evidence of fundus changes. Heparin therapy was discontinued for seven months, at the end of which time vision had again diminished to O. D. 20/50, O. S. 20/100. Another series, of 10 injections, twice weekly, was given, with the result that vision in the right eye declined to 20/200, but in the left eye it improved to 20/70. Injections were continued for another three months, using the same schedule, and by that time vision had improved to O. D. 20/100, O. S. 20/40. There followed another rest period of four months, during which left vision remained stationary while right vision declined to 20/200. A new series of injections was followed by another rest period of two months. Right vision had not improved, but left vision returned to 20/25−; no new hemorrhages or other evidence of progression of the disciform process could be observed in either eye. Since there were no deleterious effects, locally or systemically, the schedule was changed to 10 injections given in the course of five weeks, followed by a rest period of three weeks; this schedule was maintained until September, 1955. After a total of approximately 120 injections over a period of three and one-half years, corrected vision was O. D. 20/25+2, O. S. 20/25−3. Fundus photographs at that time (Figs. 1E and 1F) show the disappearance of the

---

Figs. 1A and 1B (Case 1).—Right and left fundi, respectively, June, 1956. Colloid macular degeneration, disciform involvement, and beginning pigmentary changes, bilaterally.

Figs. 1C and 1D (Case 1).—Right and left fundi, respectively, February, 1952, just before heparin therapy. Increase of disciform swelling and pigmentary changes, bilaterally.

Figs. 1E and 1F (Case 1).—Right and left fundi, respectively, September, 1955, after approximately 120 intravenous injections of heparin. Disappearance of disciform swelling and pigmentation; marked diminution of colloid bodies in central areas; color of retina more normal.

Fig. 2A (Case 17).—Right fundus, December, 1955, just before heparin therapy. Paramacular disciform lesion indicated by arrow.

Fig. 2B (Case 17).—Right fundus, February, 1956, after 20 intravenous injections of heparin. Marked diminution of disciform lesion, with only a healed, slightly pigmented scar remaining; almost complete disappearance of edema.

Figure 1A

Figure 1B

Figure 1C

Figure 1D

Figure 1E

Figure 1F

Figure 2A

Figure 2B

disciform swelling and of the pigmentation in both fundi; colloid bodies in the central areas had markedly diminished, and the color of the retina was more normal.

At first, the visual acuity in the right eye responded better to heparin therapy, but afterwards it declined to 20/200, and it remained at that extremely low level for an entire year; then it improved quickly and was in the end slightly better than in the other eye. Visual acuity of the left eye improved slowly, but progressively, and after one year's therapy it remained above 20/40.

CASE 17.—A 68-year-old male business manager was first seen in October, 1955; corrected vision was O. D. 20/30+2, O. S. 20/300. The patient reported poor left vision since childhood, but there was no history of left esotropia and no anisometropia. External eye examination was negative; media were clear; discs were normal. In the right fundus, below the superior temporal arcade, there was a poorly demarcated disciform lesion, measuring one and one-half disc diameters and extending downward to the macula. In spite of treatment with vasodilators, iodides, and a preparation containing choline, inositol, and methionine (Lipotriad), corrected right vision diminished within two months to 20/60+2; at the same time the paramacular disciform lesion in the right fundus had become more marked (Fig. 2A). On Dec. 17, 1955, intravenous heparin therapy, 100 mg. twice weekly, was begun. After 20 injections corrected vision improved to 20/25+2; the fundus photograph on Feb. 6, 1956 (Fig. 2B) shows the marked diminution in the size of the lesion and the absence of edema, with only a healed, slightly pigmented scar remaining.

CASE 20.—A 61-year-old female clerk was first seen January, 1956; vision was O. D. nil, O. S. 20/400, corrected. External eye examination was negative; right pupil was fixed to light both directly and consensually; left pupil, normal. There was right primary optic atrophy of 10 years' duration, cause unknown; the left disc was normal. Ophthalmoscopic examination of the left fundus revealed a beginning, incomplete retinal hole just below the fovea. Examination with the Zeiss slit lamp and the Hruby lens demonstrated the anterior retinal layers overlying the cyst to be intact. The left visual field showed a central scotoma for the 6, 4, and 2 mm. targets (Fig. 3A). Heparin therapy was initiated, with twice-weekly injections of 100 mg. On March 10, after 10 injections, the cyst had disappeared and the macular region presented a more normal color and configuration, with a good foveal reflex. At the same time vision had returned to 20/30−2. The very center of the scotoma had cleared for the 6 and 4 mm. targets, but there still persisted a relative scotoma for the 2 mm. target (Fig. 3B). On April 4 the clear area in the center had extended into the periphery and only a crescent-shaped paracentral scotoma remained (Fig. 3C). Heparin treatment was terminated on May 4, after a total of 25 injections; a field study at that time gave evidence of further diminution of the paracentral scotoma (Fig. 3D); visual acuity had returned to 20/25+1.

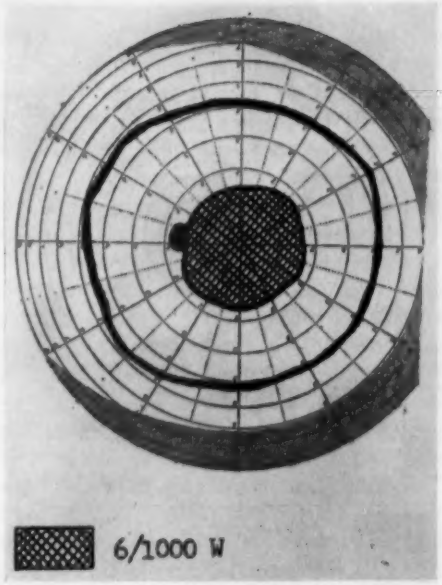


Fig. 3A (Case 20).—Left visual field, Jan. 20, 1956. Central scotoma for 6, 4, and 2 mm. targets.

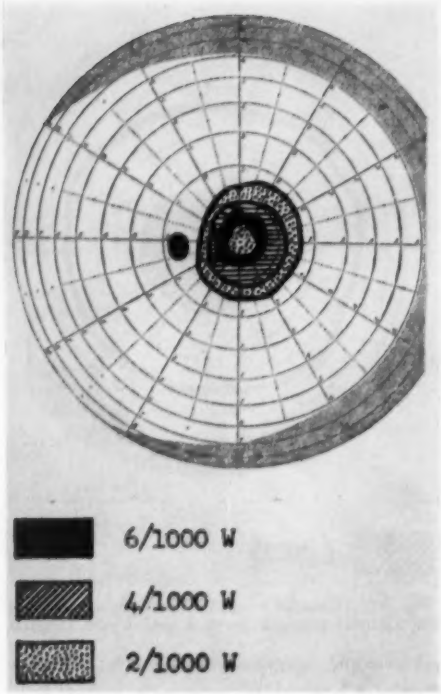


Fig. 3B (Case 20).—Left visual field, March 10, 1956, after 10 intravenous injections of heparin. In the very center the scotoma has cleared for the 6 and 4 mm. targets; paracentral relative scotoma for the 2 mm. target.

In passing, it may be mentioned that in two cases (Cases 9 and 11) uncomplicated intracapsular cataract extraction was followed by progressive diminution of central vision in the operated on eye, due to early disciform changes with minute hemorrhages. Heparin therapy resulted in improvement of vision from 20/200 to 20/25 (Case 9) and from 20/60−3 to 20/30−3 (Case 11).

Comment

In this series the cases with disciform macular degeneration, which usually causes the most rapid and profound loss of central vision, showed the best response. A definite improvement and a delay in progress were also observed in the arteriosclerotic type of macular degeneration (Haab's senile macular degeneration).[16] This difference in the response between the disciform type of macular degeneration and the arteriosclerotic type may find its explanation in observations made by Verhoeff and Grossman[17] and by Hobbs.[18] Verhoeff and Grossman demonstrated in the eye of a 63-year-old man, enucleated for probable sarcoma of the choroid, that an irregular elevated area in the macular region was due to subretinal exudate of serum; they concluded that "disciform degeneration is due to some disturbance, possibly only temporary, in the choriocapillaris of the macular region, since [observations in these cases] show the primary condition to be hemorrhage or serous exudation beneath the pigment epithelium." They suggested that some cases of senile disciform macular degeneration and the juvenile type of the lesion have probably a similar origin; in the senile form subretinal hemorrhages may occur because of associated atherosclerosis, whereas in the juvenile type only serous exudate develops, which is usually absorbed, owing to more

Fig. 3C (Case 20).—Left visual field, April 4, 1956. The central area has completely cleared; only a crescent-shaped paracentral scotoma for the 6 and 4 mm. targets remains.

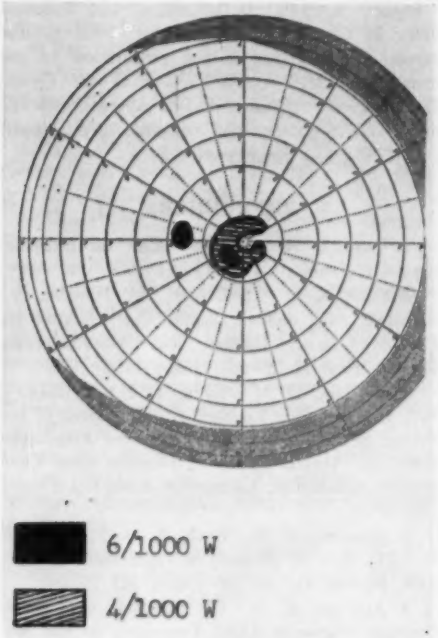


Fig. 3D (Case 20).—Left visual field, May 4, 1956, after 25 intravenous injections of heparin. The crescent-shaped paracentral scotoma for the 6 and 4 mm. targets is still further reduced.

favorable tissue response. In accepting this hypothesis, Duke-Elder [19] cautioned that it is as yet unproved and rests on circumstantial evidence. Bennett [20] also considers central serous retinopathy and disciform degeneration of the macula as related if not identical conditions. Hobbs,[18] in discussing a case of senile disciform macular degeneration which responded to cortisone therapy, remarked that the findings of Verhoeff and Grossman provide "a link between the more usual senile cases associated with a hæmorrhagic exudate and a poor prognosis for central vision, and those in which an exudative macular lesion of good visual prognosis is seen in younger individuals." Clinical evidence for the similarity of juvenile and senile disciform macular degeneration is suggested by a parallel study now in progress. Intravenous heparin, in doses of 100 mg. twice weekly, was administered to patients with central serous (angiospastic) retinopathy; a certain degree of improvement had previously been obtained by the usual treatment methods, including the steroids; heparin therapy, started after a lapse of four to six months, during which no additional improvement had occurred, resulted in further marked recovery of visual acuity, with return to completely normal central vision and fields in some cases.

The effect of heparin in these cases of senile macular degeneration may be due to any one or to a combination of its various actions. Aside from the well-known anticoagulant effect,[21] heparin exerts a fat-clearing action due to its influence on the physiological degradation of the serum lipoproteins; because of this, heparin has been shown to have an antiatherogenic effect.[22] Furthermore, heparin resolves small mural thrombi, which may play a part in the development of arteriosclerosis.[23,24] Heparin also inhibits both the local and generalized Schwartzman reactions [25]; it is, furthermore, a vasodilator.[26] In addition, injection of heparin increases the oxygen uptake in atherosclerotic patients and results in improved oxygen utilization [27]; it is suggested that this is probably due to the dissolution of larger lipoprotein molecules. Macromolecules have been shown to form films on the surfaces of the cells and the vascular intima,[28,29] thus interfering with the normal metabolic exchange between the plasma and interstitial fluid. At the present time, the available experimental and clinical evidence would seem to indicate that the lipemia-clearing action of heparin and the absorption of fat films are the mechanisms responsible for the favorable results obtained in these cases.

It is hoped that this preliminary report may stimulate further investigation on the effect of heparin in the treatment of senile macular degeneration. In the present series patients were followed with frequently repeated determinations of visual acuity, fundus examinations, and campimetric studies. At first heparin was administered only to subjects with moderately or far-advanced lesions; subsequently the therapy was ex-

tended to earlier cases, in some of which good results were obtained after a series of not more than 10 injections. In a few instances vision began to decline several months to a year after termination of treatment, but the peak of improvement was usually regained by a small series of booster injections.

A definite improvement was obtained in more than half of the cases in this series. This result is particularly significant in view of the fact that many of the lesions were far-advanced. It is probable that a series consisting of earlier cases would have shown a much higher rate of improvement. At the present time it is felt that in considering heparin therapy a distinction should be made between the arteriosclerotic and the disciform type of senile macular degeneration. Since the arteriosclerotic type progresses more slowly, it may be advisable to rely on the usual treatment methods until central vision has declined to 20/40, before initiating heparin therapy. In the disciform type of senile macular degeneration, where the visual loss is often sudden and severe, heparin therapy should be instituted as soon as the condition is diagnosed. The fact that three cases in this series remained stationary and that in three other instances the visual loss progressed during treatment should not deter one from using heparin therapy. To quote Hobbs,[18] "If the hitherto inevitably hopeless prognosis of macular lesions in older people can be altered in any degree by treatment this would appear to be an opportunity not to be disregarded."

Summary

Twenty-three patients with senile macular degeneration are presented, in whom intravenous heparin therapy was used, with moderate to marked improvement in more than half the number of cases.

The method of administration is described.

An analysis of the results is presented.

Several possibilities of the mode of action of heparin in cases of senile macular degeneration are considered.

Robert A. Sills, M.D., studied and followed many of the cases here presented; Fred E. Engreen, Ph.D., helped in the preparation of the manuscript; Mr. Zolton Yuhasz, of the Estelle Doheny Eye Foundation of Los Angeles, took the many fundus photographs incidental to this study.

1917 Wilshire Blvd. (57).

REFERENCES

1. Page, I. H.: Atherosclerosis, an Introduction, Circulation 10:1-27 (July) 1954.

2. Gofman, J. W.; Glazier, F.; Tamplin, A.; Strisower, B., and de Lalla, O.: Lipoproteins, Coronary Heart Disease, and Atherosclerosis, Physiol. Rev. 34:589-607 (July) 1954.

3. Graham, D. M.; Lyon, T. P.; Gofman, J. W.; Jones, H. B.; Yankley, A.; Simonton, J., and White, S.: Blood Lipids and Human Atherosclerosis: II. The Influence of Heparin upon Lipoprotein Metabolism, Circulation 4:666-673 (Nov.) 1951.

4. Anfinsen, C. B.; Boyle, E., and Brown, R. K.: The Role of Heparin in Lipoprotein Metabolism, Science 115:583-586 (May 30) 1952.

5. Anfinsen, C. B.: On the Role of Lipemia Clearing Factor in Lipid Transport, in Fat Metabolism: A Symposium on the Clinical and Biochemical Aspects of Fat Utilization in Health and Disease, edited by V. A. Najjar, Baltimore, The Johns Hopkins Press, 1954, pp. 93-110.

6. Engelberg, H.: Correlation of Plasma Heparin Levels with Serum Lipoproteins, Acta med. scandinav. 151:161-166, 1955.

7. Engelberg, H.: Personal communication to the author, January, 1952.

8. Maumenee, A. E.: Diseases of the Retina, A. M. A. Arch. Ophth. 49:553-586 (May) 1953.

9. Bick, M. W., and Wood, R. M.: Heparin and Ocular Hypersensitivity, J. Immunol. 64:357-364 (May) 1950.

10. Bick, M. W., and Wood, R. M.: Heparin and Uveitis, Am. J. Ophth. 33:1878-1881 (Dec.) 1950.

11. Vannas, S.: Experimental and Clinical Investigations into the Effect of Locally Administered Heparin on the Eye, Acta ophth. 31 (Supp. 40):92-93, 1953.

12. Vannas, S., cited by Berlin.[13]

13. Berlin, R.: Heparin Treatment of Diabetic Retinopathy, Acta ophth. 32:711-716, 1954.

14. Mylius, K., and Stark, H.: Untersuchungen über die Bedeutung der Arteriosklerose bei Foveaprozessen, von Graefes Arch. Ophth. 156:374-394, 1955.

15. Engelberg, H., and Massell, T. B.: Heparin in the Treatment of Advanced Peripheral Atherosclerosis, Am. J. M. Sc. 225:14-19 (Jan.) 1953.

16. Duke-Elder, W. S.: Text-Book of Ophthalmology: Vol. 3, St. Louis, The C. V. Mosby Company, 1941, p. 2372.

17. Verhoeff, F. H., and Grossman, H. P.: Pathogenesis of Disciform Degeneration of the Macula, Arch. Ophth. 18:561-585 (Oct.) 1937.

18. Hobbs, H. E.: Macular Degeneration Treated with Cortisone, Proc. Roy. Soc. Med. 46:213-218 (March) 1953.

19. Duke-Elder, W. S.: Text-Book of Ophthalmology: Vol. 3, St. Louis, The C. V. Mosby Company, 1941, p. 2116.

20. Bennett, G.: Central Serous Retinopathy, Brit. J. Ophth. 39:605-618 (Oct.) 1955.

21. Wessler, S., and Morris, L. E.: Studies in Intravascular Coagulation: IV. The Effect of Heparin and Dicumarol on Serum-Induced Venous Thrombosis, Circulation 12:553-556 (Oct.) 1955.

22. Engelberg, H.; Kuhn, R., and Steinman, M.: A Controlled Study of the Effect of Intermittent Heparin Therapy on the Course of Human Coronary Atherosclerosis, Circulation 13:489-498 (April) 1956.

23. Duguid, J. B., and Anderson, G. S. The Pathogenesis of Hyaline Arteriosclerosis, J. Path. & Bact. 64: 519-522 (July) 1952.

24. Crawford, T., and Levene, C. I.: The Incorporation of Fibrin in the Aortic Intima, J. Path. & Bact. 64:523-528 (July) 1952.

25. Good, R. A., and Thomas, L.: Studies on the Generalized Schwartzman Reaction: IV. Prevention of the Local and Generalized Schwartzman Reactions with Heparin, J. Exper. Med. 97: 871-888 (June) 1953.

26. Gilbert, N. C., and Nalefski, L. A.: The Effect of Heparin and Dicumarol in Increasing the Coronary Flow Volume, J. Lab & Clin. Med. 34:797-805 (June) 1949.

27. Engelberg, H., and Kuhn, R.: Studies of Forearm Arteriovenous Oxygen Differences in Atherosclerotic Patients Before and After Heparin, Angiology 7:73-83 (Feb.) 1956.

28. Hueper, W. C.: Arteriosclerosis: The Anoxemia Theory, Arch. Path. 39:117-122 (Feb.) 1945.

29. Cullen, C. F., and Swank, R. L.: Intravascular Aggregation and Adhesiveness of the Blood Elements Associated with Alimentary Lipemia and Injections of Large Molecular Substances: Effect on Blood-Brain Barrier, Circulation 9:335-346 (March) 1954.

An Analysis of the General Type of Uniocular Rotations

PAUL BOEDER, Ph.D., Southbridge, Mass.

Introduction

Much in the recent literature on oculorotations and Listing's law is concerned with the "false torsion" that occurs in oblique positions of the globe and with removing the misunderstandings to which this concept has given rise. The emphasis has been on oculorotations around axes in Listing's plane, and, with the aid of models and photographs of such, this type of oculorotation, from the primary position to any other, has largely been settled, although some confusion persists.[1]

It is different with oculorotations starting from positions other than the primary position. Here misconceptions are still deeply rooted—no doubt, because of the intricacy of analyzing the general case.[2-4] Thus, for instance, Tschermak-Seysenegg,[5] who constructed several ingenious models in order to elucidate the simple case of oculorotations, states in regard to the movements around secondary axes, "Every movement other than a primary radial one, whether starting from the primary or a secondary position, has an axis of rotation which does not lie in the primary axis-plane, or Listing's plane, and consequently has a component rotation about the line of sight. In other words, there is an automatic secondary effect of cyclorotation." And Duke-Elder,[6] in summing up his discussion of oculorotations of nonconverging eyes, states, "We have seen that when the eyes start from the primary position, movements into any other position are not associated with true rolling *; and we have also seen that in movements from any non-primary position a component of rolling enters into the kinematics of the eyes."

Thus, on the one hand, the authors affirm Listing's law—which demands for every position of the line of fixation an orientation of the eyeball free of cyclorotation with respect to the primary position—and, on the other, they admit cyclorotations for less easily analyzable oculorotations. But Listing's law is either valid (then there are no cyclorotations), or there are cyclorotations (then Listing's law is invalid). Surely, both assertions cannot be true at the same time. The inconsistency very likely arose because the elaborate mathematical treatments in the literature have somewhat obscured this subject. It is, however, possible to gain an insight into the mechanics of all types of oculorotations without an elaborate mathematical machinery. The object of this paper is to demonstrate this.

Brief Review of Fundamentals

In the theory of oculorotations the eyeball is regarded as a sphere rotating around its center, which is fixed in the head. Rotation around the center means that only lines that pass through the center of the sphere can serve as axes of rotation. Thus, in a full rotation around a single axis, all points on the sphere, except the poles of the axis, describe circles which lie in planes perpendicular to the axis. The circle whose plane passes through the center of the sphere is called a great circle; a circle whose plane does not pass through the center of the sphere is called a small circle (Fig. 1). If any one of these circles is known, the corresponding axis of rotation can be found by erecting, at the circle's center, the perpendicular to the plane of the circle.

Received for publication June 21, 1956.

* It is clear that cyclorotations with respect to the primary position are meant here.

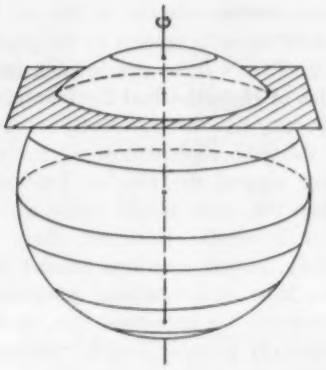


Fig. 1.—In a rotation of a sphere around an axis through its center, all points travel on circles that lie in planes perpendicular to the axis.

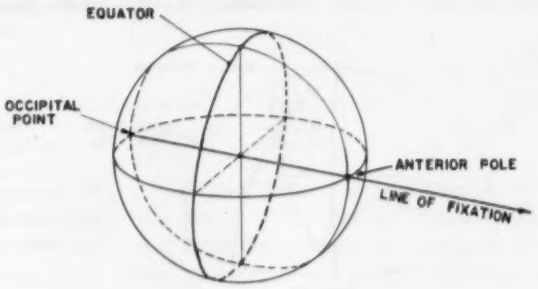


Fig. 2.—The primary position of the eye, in which the equatorial plane is assumed to be a frontal plane.

To study the movements of the eye one starts with the primary position, which is here assumed to be obtained when, with the head erect, the equatorial plane of the eye is a frontal plane, that is, when the line of fixation is horizontal and points straight ahead † (Fig. 2).

In the primary position, the line of fixation begins at the posterior pole—also called occipital point—passes through the center of rotation, and pierces the sphere at the anterior pole. The planes that pass through the line of fixation intersect the sphere in great circles called meridians.

The meridians and other landmarks of the globe in its primary position serve as a background or reference system for the rotating globe. To identify the orientations of the moving globe (and, in particular, also the orientations of the retinal meridians of the moving eye) with respect to this stationary background, a cross, consisting of a vertical and a horizontal arm, is firmly attached to the line of fixation at the anterior pole. The center of the cross, that is, the point of the line of fixation that moves on the reference globe when the eye changes fixation, shall also be called the fixation index-point.

Listing's Law

The experimentally confirmed basis for oculorotations with fixed head is Listing's law, which states:

Every movement of the eye in which the line of fixation travels from the primary position to any other position is equivalent to a simple rotation round an axis perpendicular to the meridional plane that passes through the final position of the line of fixation.

"Equivalent" means here that, regardless of the path by which the center of the cross may have reached the final position, the orientation of the cross is the same as

† In actual practice, the primary position, whose special significance in regard to oculorotations will become evident in what follows, must be determined experimentally.

that which the cross would have assumed if its center, in a rotation round a single axis, had traveled along the meridian. From this follows:

There is one and only one orientation of the eye for each direction of the line of fixation. This is Donders' law, which preceded Listing's law.

Positions on the horizontal and vertical meridians, so-called secondary positions, can be reached from the primary position by a rotation around the vertical or horizontal axis, respectively. These axes lie in the equatorial reference plane. Oblique positions, so-called tertiary positions, can be reached from the primary position by simple rotations around axes lying in the equatorial reference plane intermediate between the vertical and horizontal axes. The equatorial reference plane is also called Listing's plane.

These rotations along meridians with corresponding axes in Listing's plane are distinguished by the fact that they do not introduce cyclorotations with respect to the primary position. This is true for all meridians, even though for any tertiary position we have to accept the consequence, namely, that the cross is cyclorotated with respect to the objective vertical, that is, to the vertical great circle that passes through the tertiary position (Fig. 3). This cyclorotation has been called wheel rotation (Helmholtz), torsion (Duke-Elder), false torsion, and kinematic inclination (Tschermak-Seysenegg). Though the cross is definitely cyclorotated with respect to the vertical great circle that passes through the tertiary position, this orientation nevertheless represents the only one of the eye free of cyclorotation with respect to the primary position.‡ This will be clearly seen below.

Examples of Hypothetical Cyclorotations

The purest type of cyclorotation would occur if the only movement of the eye were a rotation around the line of fixation as axis, when the cross would rotate like the spokes of a wheel. However, there are, theoretically, simple rotations around other axes that have cyclorotational components. To demonstrate this important fact, consider all theoretically possible simple rotations—that is, rotations with a single axis each—from the primary position to a secondary position (Fig. 4). Through only two points, infinitely many circles can be drawn on the sphere, each circle representing a simple rotation round its corresponding axis. The angles which the arms of the cross make

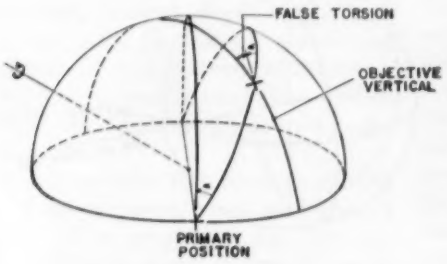


Fig. 3.—Simple rotations around axes in Listing's plane induce no cyclorotation with respect to the primary position, although oblique rotations induce "false torsion," that is, cyclorotations with respect to objective verticals.

‡ Actually, it is meaningless to speak of cyclorotation without stating the reference. Thus, the two statements (1) for each tertiary position there is a certain amount of torsion (or cyclorotation with respect to the corresponding objective vertical) and (2) all positions of the eye are free of cyclorotation (with respect to the primary position) are both correct if the qualifications in the parentheses are added. Without these qualifications, the statements are contradictory, and, therefore, have led to untold confusion. It is doubtful whether the introduction of a differentiating term, torsion or false torsion, in artificial contradistinction to cyclorotation or rolling, has helped matters. It would have been more illuminating to avoid an extra term and simply to state the reference. In a discussion, this would have to be done only once, unless the reference is changed repeatedly. Thus in this paper, whenever cyclorotation is used without qualification, cyclorotation with respect to the primary position is meant.

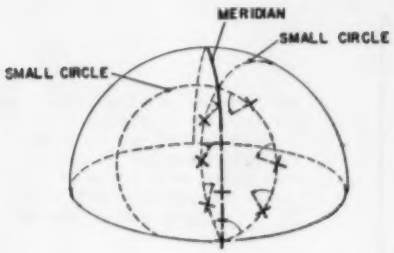


Fig. 4.—Among all theoretically possible simple rotations of the globe from the primary position to a secondary (or any other) position, the rotation along the meridian is the only one that does not induce a cyclorotation with respect to the primary position.

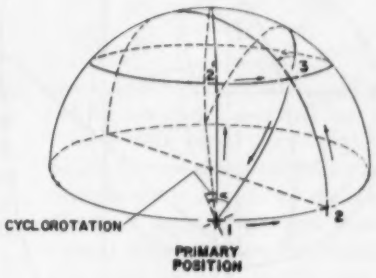


Fig. 5.—The cyclorotation (indicated by the dashed cross at *1*) induced by the hypothetical simple rotation along the great vertical circle from *2* to *3* is the same as that induced by the hypothetical simple rotation along the horizontal small circle from *2'* to *3*.

with the circle along which the center of the cross travels cannot change in a simple rotation. The result is that the cross would be tilted—cyclorotated—for all simple rotations from the primary to the secondary position except for the rotation along the meridian.

In a further hypothetical example of "induced" cyclorotation with respect to the primary position, let the line of fixation rotate to a secondary position on the horizontal meridian, then along a vertical great circle to a tertiary position, and finally back along the meridian into the primary position (Fig. 5). Remembering that the angles which the arms of the cross make with the circle along which the fixation index-point travels cannot change in a simple rotation, we find that the cross arrives at the primary position—cyclorotated. Since the rotations along the meridians do not induce cyclorotation, it must have been induced by the hypothetical rotation along the great vertical circle. It should be noted that if there is, as in this example, no cyclorotation (false torsion) with respect to the objective vertical through the tertiary position, there is cyclorotation with respect to the primary position, and vice versa.

The same amount of cyclorotation would be induced if the line of fixation rotated first from the primary position to a secondary position on the vertical meridian, then along a small horizontal circle to the same tertiary point as before, and finally back to the primary position along the meridian. Here the resulting cyclorotation is induced by the hypothetical rotation along the horizontal small circle, in spite of the fact that its corresponding vertical axis lies in Listing's plane.

The Solution of the General Problem of Oculorotations

Listing's law excludes all cyclorotations with respect to the primary position, pure as well as induced ones, and so the general problem regarding the movements of the single eye is to find those rotations that are free of cyclorotation with respect to the primary position. This thorny mathematical problem in spherical kinematics becomes surprisingly simple if we seek the solution via a plane map of the globe.

Let us make such a map by projecting from the occipital point, that is, from the posterior pole of the eye, onto a plane

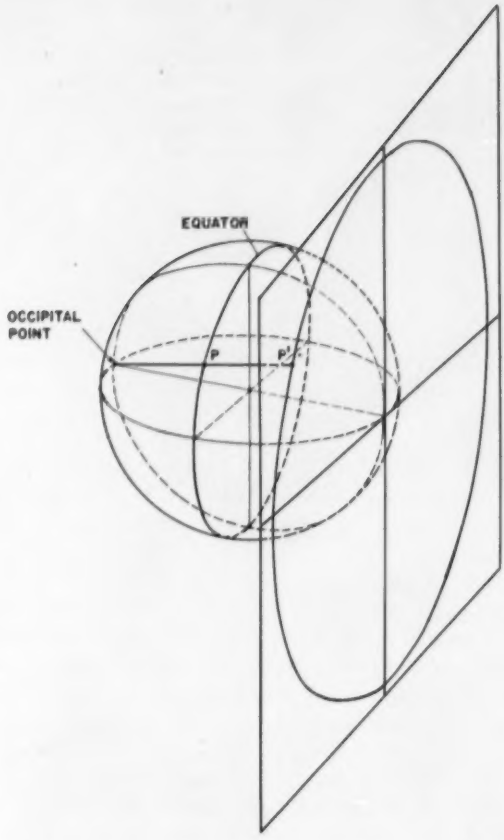


Fig. 6.—A plane map of the globe in the primary position can be made by projecting from the occipital point onto a plane that is tangent at the anterior pole. The equator is mapped into a circle; all circles through the occipital point are mapped into straight lines.

which is tangent to the sphere at the anterior pole (Fig. 6). This is the well-known stereographic projection which is used in mapping the points of the earth onto a plane. It is at once clear that the equator of the eye will give rise to a circle in the plane; that the meridians, since their planes pass through the point of projection, will be straight lines through the center; that, in fact, all circles through the occipital point (since their planes also pass through the point of projection) will give rise to straight lines in the plane, and that all circles not passing through the occipital point will not give rise to straight lines.

It is not so obvious, but will be accepted here without proof, that all circles on the globe not passing through the occipital point will give rise to circles in the plane and that all angles on the sphere will be represented without distortion in the map.

Now, if the cross moves, in accordance with Listing's law, from the primary position in a simple rotation along any meridian, it will always remain upright in the map; there is no cyclorotation with respect to the primary position. Referred to the map, Donders' law reads as follows: For every position of the line of fixation, the cross is upright. If, in any tertiary position, this upright orientation of the cross is compared with the objective vertical through this position, that is, with a vertical great circle which is also a circle in the map, then the "false torsion" will show up in exactly the same angular amount as on the sphere (Fig. 7).

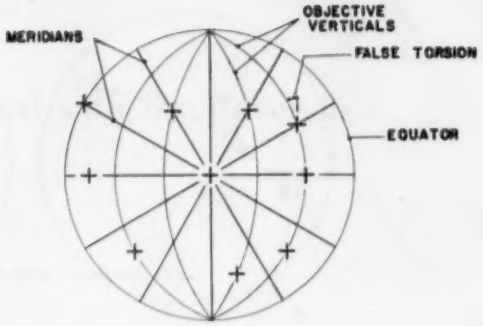


Fig. 7.—Listing's law demands that the cross is upright in the map for all positions of the line of fixation. False torsion is the angle that the vertical arm of the cross makes with the circles that represent the objective verticals in the map.

In reference to the map, we can make further the following statement: Without violating Listing's law, the eye can execute only those rotations which permit the cross to be upright at all points of the path. Let us consider any two points in the map. The simplest path that leads from one point to the other, without changing the upright position of the cross, is the straight line connecting the two points (Fig. 8). On the sphere, this straight line corresponds to a circle that passes through the occipital point and the two points that mark the two positions of the line of fixations, that is, the two fixation index-points. Therefore, Listing's law, extended, is as follows:

Every movement of the eye in which the line of fixation travels from one position to another is equivalent to a simple rotation round the axis of the circle that passes through the occipital point and the two fixation index-points.

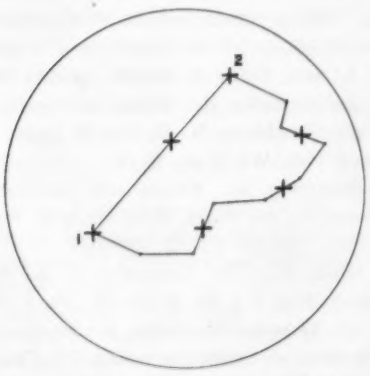


Fig. 8.—In changing fixation from *1* to *2*, cyclorotation is avoided on those paths in the map that consist of line segments which, on the globe, correspond to arcs of circles through the occipital point.

Helmholtz called the circles through the occipital point direction circles because they correspond to curves in the field of view that have apparent constant directions. The axis of rotation that corresponds to a direction circle lies in Listing's plane only if the circle happens to be a great circle, that is, a meridian. For all small direction circles, the corresponding axes are inclined to Listing's plane.§ We should note further that only in rotations along meridians does the line of fixation remain in a plane; along all small direction circles the line of fixation describes a cone with its vertex at the center of rotation.

A less direct way of traveling from one point in the map to another, with the cross in an upright position at all points of the path, is one which connects the two points by a series of small straight line segments (Fig. 8). Each of these line segments represents a part of a direction circle, each of which has its own axis. In other words, the axis of rotation in the eye will have to change from line segment to line segment. Assuming that this change of axis can be executed by the eye with sufficient fineness

§ From the map, the axis of rotation corresponding to a direction circle can readily be located as follows: It lies in the meridian plane that is perpendicular to the line trace of the direction circle in question, and its inclination, α, to Listing's plane is determined by $\tan\alpha = a/r$, where a is the distance of the line trace from the center and r is the radius of the circle representing the equator in the map.

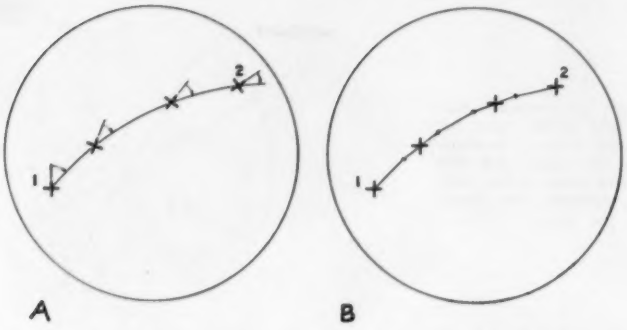


Fig. 9.—*A*, a simple rotation along a great circle (not a meridian) induces cyclorotation; *B*, cyclorotation is avoided along line segments approximating the arc of the great circle (or any other curved path).

and accuracy, the individual line segments could be smaller and more numerous, so that any conceivable curved path on the sphere can be followed by the index-point of the line of fixation. But it must be remembered that this is accomplished exclusively by rotations along arcs of direction circles that correspond to the line segments in the map.

As an example, let the two points indicating two positions of the line of fixation, not in the same meridian, be connected on the sphere by an arc of a great circle. In the map, this great circle, since it does not pass through the occipital point, is represented by a circle through the two points that represent the two positions. A simple rotation round the axis of the great circle would tilt the cross in the map (Fig. 9*A*).

However, it is nevertheless possible for the line of fixation to follow the path of the great circle by traveling along small arcs of direction circles approximating the great circle; in other words, by constantly changing the axis of rotation in order to avoid cyclorotation with respect to the primary position (Fig. 9*B*). In the ideal case, the direction circle employed at a given point of a curved path is represented in the map by the tangent to the curve, and one can speak of an instantaneous axis of rotation at this point. On the sphere, this means that any curved path can be followed by the line of fixation, without cyclorotation, provided the actual rotations are along direction circles that are tangent to the curved path.

In short, the eye changes fixation only along circles through the occipital point.

This restriction—this reduction of the degrees of freedom of oculorotation from three to two—has the remarkable advantage of insuring, for every fixation of the globe, a reproducible orientation, free of cyclorotations with respect to the primary position, no matter from which position and on which path the fixation is reached.

American Optical Company.

REFERENCES

1. Linksz, A.: Ocular Axes and Meridians During Oblique Oculorotations: A Contribution to the Problem of So-Called False Torsion, A. M. A. Arch. Ophth. 55:380-396 (March) 1956.

2. von Helmholtz, H.: Treatise on Physiological Optics, Rochester, N. Y., Optical Society of America, 1925, Vol. 3, pp. 71-107.

3. Burmester, L.: Kinematische Aufklärung der Bewegung des Auges, München Acad. Wiss., math.-phys. Kl., pp. 171-202, 1918-1919.

4. Lamb, H.: The Kinematics of the Eye, Philosoph. Mag. & J. Sc. 38:685-695 (Dec.) 1919.

5. von Tschermak-Seysenegg, A.: Introduction to Physiological Optics, Springfield, Ill., Charles C Thomas, Publisher, 1952, p. 256.

6. Duke-Elder, W. S.: Textbook of Ophthalmology: Vol. 1, St. Louis, The C. V. Mosby Company, 1939, p. 601.

Lens Metabolism as Studied with the Reversible Cation Shift

III. The Effect of Lens Age (Size)

DANIEL J. HEINRICHS, M.D., and JOHN E. HARRIS, M.D., Portland, Ore.

There is evidence to suggest that the response of the lens to certain physiologic or metabolic stresses varies with the lens age. The observation is of more than passing interest. The immediate importance of such information concerns its application to various in vivo and in vitro experimental situations. The ultimate value would conceivably stem from the application of such studies to an understanding of the senile process, specifically the senile cataract. Important among these observations are the following:

First, the age of the lens influences its response in vitro to the physiologic stress induced by cold. If the isolated rabbit lens is refrigerated at 0 C, it loses potassium and gains sodium and water; when subsequently incubated at 37 C, the sodium is excreted from the lens and the potassium reenters the lens, the movement of both cations being against a concentration gradient. This migration of cations against a gradient is reduced in older lenses.[1]

Second, there is suggestive evidence that the age of the lens significantly alters its responses to high glucose levels. Thus, the age of the animal influences the development of diabetic cataract. The younger the diabetic animal the more rapid and certain the onset of cataract.[2,3] At least one responsible factor in the development of these cataracts is the carbohydrate plethora.[4]

Third, while examining the effect of known metabolites of glucose on cation transport it became apparent that the response of the lens to the deprivation of glucose varied with the lens age.

The suggestive observations that the lens' response to various glucose levels varies with the lens age prompted the present studies of the influence of the glucose level on the cation transport in lenses of various sizes.

Materials and Methods

Fresh intact rabbit lenses were used throughout. Generally eyes were obtained from a rabbit meat company. They were enucleated immediately after death by decapitation, placed in ice-cold saline, and transported to the laboratory packed in ice. With aseptic precautions, the lenses were removed within one hour of the death of the animal. Extraction was accomplished by incising and turning back the sclera, removing the vitreous with a lens loop, and carefully cutting the zonules with a sharp scissors. In this procedure particular care was taken to avoid touching the lens surface with the lens loop or scissors. The isolated lens, resting on its posterior surface, was placed in a sterile tube containing 3 ml.

Received for publication July 5, 1956.

From the John E. Weeks Memorial Laboratory, Department of Ophthalmology, University of Oregon Medical School.

Supported by Grant B-187 from the National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Md.

Part of a thesis submitted by Dr. Heinrichs to the Graduate Council of the University of Oregon Medical School in partial fulfillment of the requirements for the degree of Master of Science.

of the appropriate medium.* The tubes were flushed with a mixture of 95% oxygen and 5% carbon dioxide (95% nitrogen and 5% carbon dioxide when anaerobic conditions were imposed), tightly stoppered, and placed in an ice-bath at 0 C. After refrigeration for 40 to 44 hours one lens of each pair was analyzed immediately, while the other was transferred to a water bath at 37 C and incubated for an additional six hours before analysis. For the purpose of exposition this experimental procedure is listed as a "cation recovery" experiment. In other instances lenses were incubated at 37 C directly for periods of 20 to 48 hours without prior refrigeration.

For each analysis the lens was blotted lightly to remove surface moisture, weighed rapidly, and placed in a drying oven for 48 hours at 105 C. The dried material was weighed and dry-ashed with the aid of a drop of concentrated sulphuric acid. For sodium and potassium determinations a Baird Associates flame photometer with an internal standard was employed.

Results of the recovery experiments are generally expressed as per cent recovery (Fig. 1).† This Figure provides a reasonably adequate expression of the ability of the refrigerated lens to return to the normal steady-state, that is, to regain its original sodium and potassium concentrations.[5]

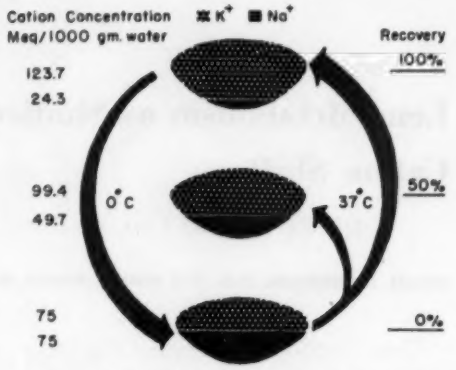


Fig. 1.—Schematic representation of the changes in cation concentrations of rabbit lenses during refrigeration at 0 C and subsequent incubation at 37 C.

Results

Variation of Cation Concentration of Fresh Lenses with Lens Age (Size).—The sodium and potassium concentrations of fresh lenses of varying size are indicated in Figure 2. No appreciable difference in cation concentration in fresh lenses was found in the size range studied. The figures for the water content are not indicated. They agree substantially with those of Ely.[6]

Lens size is here recorded in terms of dry weight. The lens continues to grow throughout life, and the relationship between the age of albino rabbits and the size of the lens has been established.[7] By use of these data it can be computed that the age range here analyzed was from 4 weeks to 12 months.

The Effect of Lens Age (Size) on Cation Recovery in Vitro.—Lenses of various sizes were incubated in the modified Tyrode's solution. The extent to which the lenses recovered original cation concentrations during incubation at 37 C following refrigeration at 0 C was observed to be inversely proportional to the size of the lens. Sodium and potassium transport appeared to be equally affected. Thus, lenses obtained from 4- to 6-week-old albino rabbits recovered completely the original cation concentrations, whereas lenses obtained from 4- to 12-month-old albino rabbits re-

* Unless otherwise stated, the medium consisted of Tyrode's solution modified to contain 148 mEq/liter sodium, 5 mEq/liter potassium, 30 mEq/liter bicarbonate, and 200 mg/100 cc. glucose. The pH of the medium was adjusted to physiologic range (pH 7.32-7.48) and checked at the end of each procedure. Osmotic pressure of the medium was maintained constant at the equivalent of 315 milliosmoles/liter as determined on a Fiske Associates osmometer. The sodium and potassium concentrations of all media were checked by analysis.

† The formula for the determination of cation recovery is the following:

$$\text{per cent recovery} = \frac{C^t - C^o}{C^i - C^o} \times 100$$

where C^t, C^o, and C^i are the concentrations after refrigeration plus incubation at 37 C, the concentrations after refrigeration alone, and the concentrations in fresh lenses, respectively.

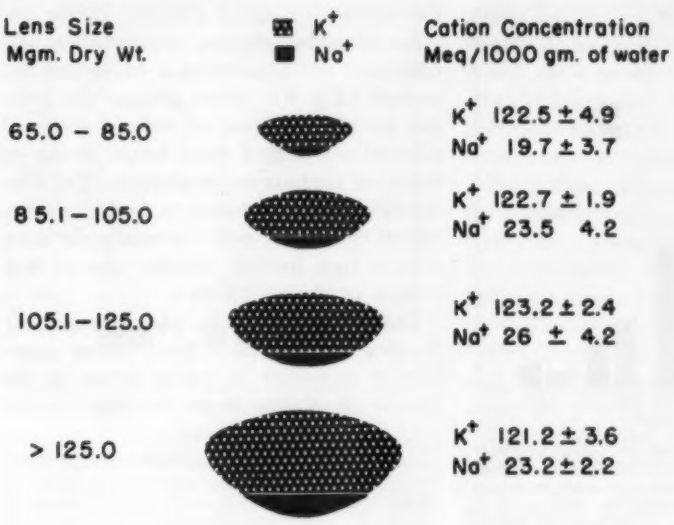


Fig. 2.—Effect of lens age (size) on the concentrations of sodium and potassium in fresh rabbit lenses. Each figure represents the average of at least eight analyses.

covered approximately 50% of the original cation concentrations (Fig. 3).

The Effect of Lens Age (Size) on Cation Recovery when Incubated in the Presence of High Glucose Concentrations.—Lenses of various sizes were subjected to the temperature changes in the usual manner in a medium containing 500 mg/100 cc. glucose. No exact correlation between the effect of high glucose concentrations and the age of the lens was observed, although cation recovery was altered in each size of lens studied (Fig. 4). The recovery of potassium concentrations was uniformly reduced, while the movement of sodium was not reduced. Indeed, the final sodium concentrations were less than those observed in fresh lenses. The results, therefore, demonstrated a sharp dissociation of the movement of sodium and potassium.

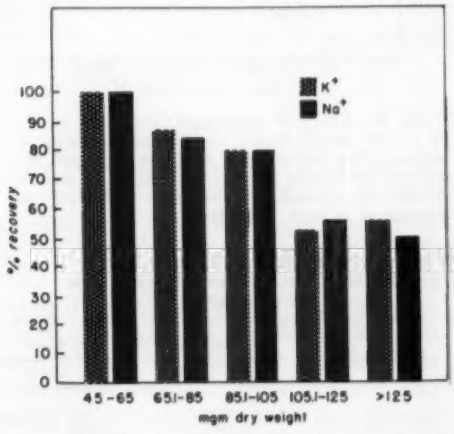


Fig. 3.—Effect of lens age on cation recovery of rabbit lenses during incubation at 37 C following a cold-induced cation shift in a medium containing 200 mg/100 cc. glucose. Each bar represents the average of at least 10 experiments involving 10 pairs of lenses.

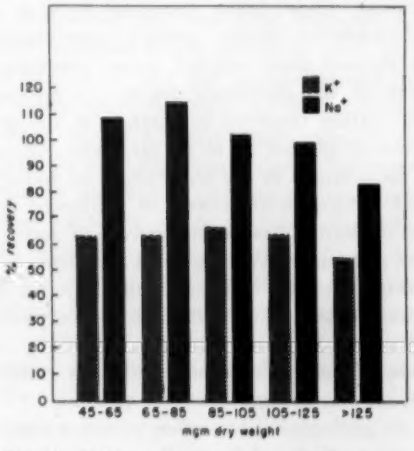


Fig. 4.—Effect of lens age on cation recovery of rabbit lenses during incubation at 37 C following a cold-induced cation shift in a medium containing 500 mg/100 cc. glucose. Each bar represents the average of at least 10 experiments involving 10 pairs of lenses.

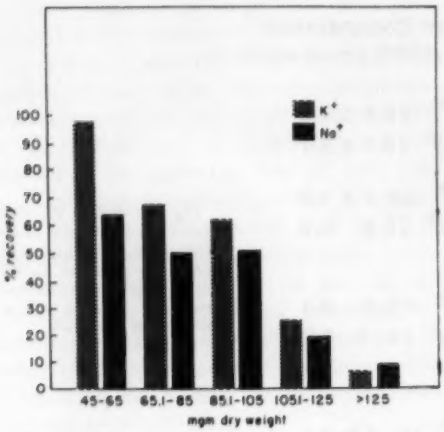


Fig. 5.—Effect of lens age on cation recovery of rabbit lenses during incubation at 37 C following a cold-induced cation shift in a medium devoid of glucose. Each bar represents the average of at least 10 experiments involving 10 pairs of lenses.

The Effect of Lens Age (Size) on Cation Transport in Vitro in the Absence of Added Glucose.—Lenses of various sizes were incubated in the usual manner after refrigeration in a medium devoid of glucose (Fig. 5). Young lenses (obtained from 4- to 6-week-old albino rabbits) recovered their original cation concentrations to a certain extent during incubation at 37 C following refrigeration at 0 C in the absence of added glucose. Older lenses (obtained from 4- to 12-month-old albino rabbits) were unable to recover their original cation concentrations to any significant degree. In no case was cation recovery as marked in the absence of glucose as in its presence. Again, a dissociation in the movements of sodium and potassium occurred, as evidenced by the disparity in per cent recovery of sodium and potassium. When glucose was deprived, sodium recovery was markedly reduced in each lens size while potassium recovery was influenced to a lesser degree, especially in young lenses, when compared with results obtained when glucose was present.

An analogous dissociation in cation transport was observed during the course of continuous incubation at 37 C. In these experiments lenses were incubated at 37 C directly, without previous refrigeration, in the absence of added glucose. In the absence of added glucose, as incubation was continued the concentration of sodium increased (Fig. 6). When glucose was present the concentration of sodium remained substantially that of fresh lenses during 40 hours of continuous incubation. The concentrations of potassium in both instances tended to rise but were essentially the same at each time interval whether glucose was present or absent (Table).

Cation Recovery in the Absence of Oxygen and Glucose.—Since cation transport is supported in young lenses in the absence of glucose under the experimental

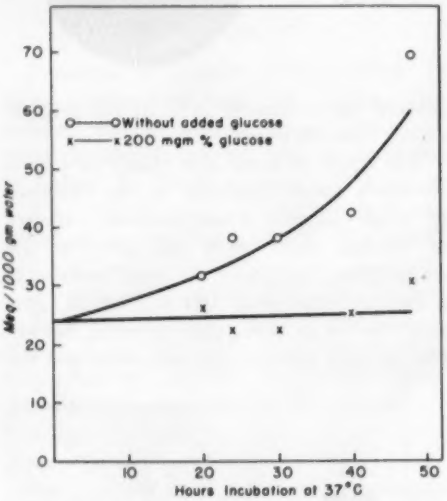


Fig. 6.—Effect of continuous incubation at 37 C of paired rabbit lenses on the concentration of sodium. One lens of each pair was incubated in a medium containing glucose, the other in a medium devoid of glucose. Each point represents the average of at least 10 analyses.

Effect of Continuous Incubation at 37 C of Paired Rabbit Lenses on the Concentration of Potassium *

Incubation, Hr.	Potassium, mEq./1000 Gm. Water	
	200 Mg./Glucose	Without Added Glucose
20	127.0	138.7
24	133.1	130.0
30	126.7	127.2
40	144.0	141.9
48	132.4	99.5

* One lens of each pair was incubated in a medium containing glucose; the other, in a medium devoid of glucose. Each value represents the average of at least 10 analyses.

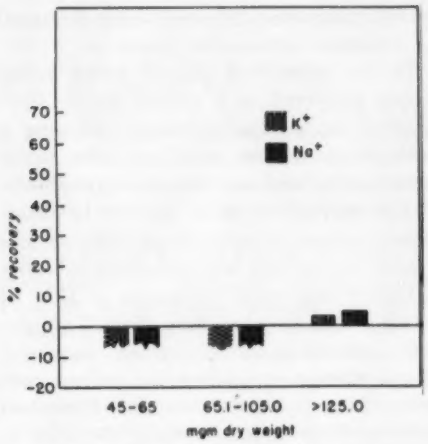


Fig. 7.—Effect of lens age on cation recovery of rabbit lenses during incubation at 37 C following a cold-induced cation shift in a medium devoid of glucose under anaerobic conditions. Each bar represents the average of at least five experiments involving five pairs of lenses.

situation, it seemed reasonable to assume that the required energy was derived from the oxidation via terminal aerobic oxidative pathways of some metabolite, perhaps lactate. To test this hypothesis the cation recovery of lenses of various sizes was measured under anaerobic conditions in a medium devoid of glucose or any other source of energy. Cation recovery was observed to be abolished in all lens sizes studied (Fig. 7). Sodium and potassium recovery were equally affected.

Comment

The inverse relationship of cation recovery to lens age in the presence of added glucose is of more than passing interest. The most obvious explanation of this finding is that the metabolic activity of young lenses is greater than that of the older ones. There is a good deal of evidence that this may be true. Glycolytic activity has been shown to be greater in young lenses.[8,9] The ability of aqueous extracts of lens homogenates to metabolize hexose phosphate to triose phosphate is reduced in older lenses.[10] It has recently been shown that young lenses incorporate a greater amount of radioactive phosphorus from the incubating medium than old lenses.[11] (This increase is reflected in a greater incorporation of P^{32} into the inorganic phosphate and adenosine triphosphate (ATP) fractions as demonstrated by electrophoretic studies.[12])

In the final analysis, the immediate energy for cation transport must derive from the high-energy phosphates. In a recent study, the relationship between cation transport and the concentrations of the various phosphate fractions in the lens was studied.[13] No exact correlation between cation transport and the concentrations of the various phosphate fractions was observed.

The thought that reduced cation recovery in older lenses is due to a reduced metabolic level is not free of objections. Major among them is the finding that the concentration of cations is not altered as age advances, as would be anticipated. The most inclusive statement that can be made from the vantage of our present knowledge is that the older lenses are not as well able as young lenses to withstand the stress imposed by cold. The ability of younger lenses to recover from this stress may result from an availability of alternate metabolic pathways. The results obtained when glucose is deleted from the incubating medium are compatible with that view, since young lenses maintain cation transport to a certain degree. Under the stress imposed by the experimental situation this demonstrated viability of the younger lenses may result from the fact that they possess alternate metabolic pathways, involving terminal oxidative pathways, which are not utilized by older lenses.

Probably the most intriguing result here reported has been the clear-cut observation that separable sodium and potassium "pumps" exist. It has been the predominate opinion of those interested in the movements of cation across cellular barriers that the movements of sodium and potassium are equivalent and that the active transport of sodium alone is required.[14] Previous studies of the lens,[1,5,15,16] erythrocyte,[17] and frog

muscle [18] have essentially supported this thesis. It is apparent, however, from the present studies that the two may be sharply dissociated and that independent secretory movements of the two ions may coexist.

Recent studies of other cells have permitted essentially the same conclusion. In particular, separate independent mechanisms regulating sodium and potassium distribution in marine algae, both dependent upon cellular metabolism, have been reported.[19] More recent examination of sodium and potassium movements in erythrocytes [20] and nerve axons [21] have indicated that although there is evidence for a coupling between the movements of sodium and potassium their movements are not rigidly linked and that a portion of the movement of each is independent of the other.

Present studies would suggest that a similar situation prevails in the lens under the conditions of the experiments. A portion of the movement of the two appears to be linked and the remainder independent. It is particularly interesting that the unlinked portion of potassium movements may not require glucose in younger lenses, whereas the independent movement of sodium is definitely dependent upon an exogenous glucose supply.

Summary

The concentration of sodium and potassium in the fresh rabbit lens was not observed to vary appreciably with lens age.

The extent to which recovery of rabbit lenses to normal cation concentrations occurred during incubation at 37 C following a cold-induced cation shift was observed to bear an inverse relationship to the age of the lens.

The extent of recovery of normal cation concentrations of rabbit lenses during incubation at 37 C following a cold-induced cation shift in a medium containing 500 mg/100 cc. glucose was not observed to vary appreciably with the age of the lens. A dissociation in cation movements was observed, potassium recovery being decreased as compared with sodium recovery.

In the absence of glucose young rabbit lenses recovered to a certain degree their original cation concentrations following a cold-induced cation shift; in older rabbit lenses cation recovery was less appreciable. Cation movements were seen to be dissociated, sodium recovery being reduced to a greater degree than was potassium recovery.

During continuous incubation at 37 C of rabbit lenses in a medium devoid of glucose, concentration of sodium increased. When glucose was added the sodium concentration remained constant. Potassium concentrations were essentially the same in the absence of glucose as in its presence.

Cation recovery of rabbit lenses of all sizes was abolished when they were incubated at 37 C following a cold-induced cation shift in a medium devoid of glucose under anaerobic conditions.

It is concluded that (*a*) the different responses of young as compared with older lenses may be due to the utilization of different metabolic pathways by young lenses; (*b*) the active transport of potassium and sodium across the lenticular barriers may be at least partially dissociated.

3181 S. W. Sam Jackson Pk. Rd.

REFERENCES

1. Harris, J. E., and Nordquist, L. T.: Factors Affecting the Cation and Water Balance of the Lens, Acta XVII Conc. Ophth. 1:1002-1012, 1954.

2. Patterson, J. W.: Cataracts Caused by Carbohydrates, Am. J. Ophth. 36:143-149 (June, Pt. 2) 1953.

3. Charalampous, F. D., and Hogsted, D. M.: Effect of Age and Diet on Development of Cataracts in the Diabetic Rat, Am. J. Physiol. 161: 540-544, 1950.

4. Patterson, J. W.: Effect of Lowered Blood Sugar on Development of Diabetic Cataracts, Am. J. Physiol. 172:77-82, 1953.

5. Harris, J. E.; Gehrsitz, L. B., and Nordquist, L.: The in Vitro Reversal of the Lenticular Cation Shift Induced by Cold or Calcium Deficiency, Am. J. Ophth. 36:39-50 (June, Pt. 2) 1953.

6. Ely, L. O.: Metabolism of the Crystalline Lens: I. Water Content and Growth Rate, Am. J. Ophth. 32:215-219 (June, Pt. 2) 1949.

7. Krause, A. C.: Chemistry of the Lens: VII. Growth and Senescence, Arch. Ophth. 13:71-77, 1935.

8. Weekers, R.: L'Acide lactique du cristallin, Arch. opht. 1:707-717, 1937.

9. Leinfelder, P. J., and Christianson, G. S.: A Critical Study of Lens Metabolism: II. Glycolysis, Am. J. Ophth. 35:33-38 (May, Pt. 2) 1952.

10. Müller, H. K.: Über die Altersveränderungen der Glykolyse in der Linse, Arch. Augenh. 110: 206-215, 1936.

11. Müller, H. K., and Kleifeld, O.: Über den Mechanismus des Eindringens von radioaktivem Phosphor in die Linsen jüngerer und älterer Kaninchen, Klin. Wchnschr. 30:662-663, 1952.

12. Müller, H. K., and Kleifeld, O.: Papierelektrophoretische Untersuchungen des Phosphatstoffwechsels der Linse jüngerer und älterer Tiere mit radioaktivem Phosphor, von Graefes Arch. Ophth. 154:165-176, 1953.

13. Hauschildt, J. D.; Harris, J. E., and Nordquist, L. T.: Changes in the Phosphate Fractions of the Lens Under Various Conditions Which Influence Cation Transport, Am. J. Ophth. 39:155-160 (Feb., Pt. 2) 1955.

14. Fenn, W. O.: Introduction to a Symposium on the Metabolism of Potassium, Journal-Lancet 73:163-166, 1953.

15. Harris, J. E.; Hauschildt, J. D., and Nordquist, L. T.: Lens Metabolism as Studied with the Reversible Cation Shift: I. The Role of Glucose, Am. J. Ophth. 38:141-147 (July, Pt. 2) 1954.

16. Harris, J. E.; Hauschildt, J. D., and Nordquist, L. T.: Lens Metabolism as Studied with the Reversible Cation Shift: II. The Effect of Oxygen and Glutamic Acid, Am. J. Ophth. 38:148-151 (July, Pt. 2) 1954.

17. Flynn, F., and Maizels, M.: Cation Control in Human Erythrocytes, J. Physiol. 110:301-318, 1950.

18. Steinbach, H. B.: On the Sodium and Potassium Balance of Isolated Frog Muscles, Proc. Nat. Acad. Sc. 39:451-454, 1952.

19. Scott, G. T., and Hayward, H. R.: Evidence for the Presence of Separate Mechanisms Regulating Potassium and Sodium Distribution in Ulva Lactuca, J. Gen. Physiol. 37:601-620, 1954.

20. Glynn, I. M.: Linked Sodium and Potassium Movements in Human Red Cells, J. Physiol. 126: 35P, 1954.

21. Hodgkin, A. L., and Keynes, H. D.: Active Transport of Cations in Giant Axons from Sepia, and Loligo, J. Physiol. 128:28-60, 1955.

The Treatment of Trachoma with Subconjunctival Injections of Chloramphenicol

R. W. B. HOLLAND, M.B., Quetta, Baluchistan, Pakistan

Chloramphenicol (Chloromycetin), administered either orally or as a 1% ointment, has been shown to be an effective therapeutic agent in the treatment of trachoma (Holland, 1954). The quickest and most efficient method of securing high tissue concentration of the antibiotic for arresting the disease is a combination of local and oral treatment.

This method also presents many advantages both in simplicity and ease of administration, for there are few patients who cannot take 4 to 6 capsules of chloramphenicol daily for 10 days and apply the ointment to their eyes four times a day for a month or two. But the main drawback to this treatment is its expense. If the capsules are omitted to reduce this expense, then the application of the ointment must be continued for a minimum of five months. This prolonged treatment is enough to daunt many who have neither the patience nor the persistence to continue with treatment for longer than a month or two. Consequently, relapses are all too common, and the medicament, not the lack of persistence on the part of the patient, is usually held to blame.

In Pakistan, most of the hospital patients with trachoma are poor villagers and townsfolk for whom prolonged or otherwise costly treatment is impractical. For these people, a low-cost, short-term treatment had to be devised that would ensure maintenance of an effective concentration of chloramphenicol in the affected tissues until the disease had been arrested. A subconjunctival injection of microcrystalline chloramphenicol seemed to be the ideal method of achieving this. Accordingly, a small-scale investigation was begun at our annual ophthalmological clinic at Shikarpur in January, 1955, to inquire into the effects of subconjunctival injections of chloramphenicol in active trachoma.

Received for publication July 27, 1956.

C. M. S. Hospital.

Materials and Methods

Since the supply of chloramphenicol for subconjunctival injection was exceeded many times by the number of patients suffering from trachoma, it was obvious that a rigid selection had to be made. Therefore only the most advanced cases of active trachoma were selected for this treatment. It soon became evident that the severity of the reactions subsequent to the injections might deter patients with early or mild cases from persisting with treatment and that we were right in reserving this rather violent method of treatment for those with really severe and active trachoma.

It is important to emphasize that no collateral treatment capable of affecting the course of the disease was used. Antibiotics were not used orally, and surgical treatment was not employed.

The first few patients were treated with a subconjunctival injection into the upper fornix of the eye, 0.5 gm. chloramphenicol suspended in 1 cc. of a solution of 1:2000 dibucaine (Nupercaine) hydrochloride. Owing to the violence of the reactions produced, this dose was subsequently halved, but the reactions did not diminish.

The following treatment was standardized later. The conjunctiva was anesthetized by instilling drops of an 0.5% solution of tetracaine (Anethaine; Amethocaine; Pontocaine) hydrochloride three times at three- to five-minute intervals. Then 1 gm. of chloramphenicol microcrystals was suspended in 2 cc. of a solution of 1:2000

Summary of Data

Case No.	State on Admission		Injections, No.	Duration of Treatment, Days	Nature of Reaction	Result
	Lids	Cornea				
88	R. granular Grade 4	Pannus Grade 4	5	21	Very severe	Greatly improved (granules disappeared, lids smooth, pannus infiltration greatly diminished)
88	L. granular Grade 4	Pannus Grade 4	5	21	Very severe	Greatly improved
100	R. granular Grade 3	Pannus Grade 3	4	17	Very severe	Greatly improved
100	L. granular Grade 3	Pannus Grade 3	4	17	Very severe	Greatly improved
131	R. granular Grade 3	Pannus and ulceration Grade 3	2	4	Severe	Improved; ulcer healed; left hospital without permission
170	R. granular Grade 3	Pannus Grade 4	8	20	Severe	Improved 50%
170	L. granular Grade 3	Pannus Grade 4	8	20	Severe	Improved 50%
548	R. granular Grade 4	Pannus Grade 4	5	10	Severe	Not improved
548	L. granular Grade 4	Pannus Grade 4	5	10	Severe	Not improved
Outpatient	R. granular Grade 3	Pannus Grade 4	2	12	Extremely severe	Greatly improved
Outpatient	L. granular Grade 3	Pannus Grade 4	2	12	Extremely severe	Greatly improved
624	R. granular Grade 4	Pannus Grade 4	3	7	Moderate	Improved 30%
624	L. granular Grade 4	Pannus Grade 4	3	7	Moderate	Improved 30%
625	R. granular Grade 4	Pannus Grade 4	1	1	Severe	Left hospital without permission
625	L. granular Grade 4	Pannus Grade 4	1	1	Severe	Left hospital without permission
640	R. granular Grade 4	Pannus Grade 4	1	7	Extremely severe	Improved 30%; left hospital without permission
640	L. granular Grade 4	Pannus Grade 4	1	7	Extremely severe	Improved 30%; left hospital without permission
648	R. granular Grade 4	Pannus Grade 4	2	10	Extremely severe	Granulations still grade 3; pannus greatly diminished
648	L. granular Grade 4	Pannus Grade 4	2	10	Extremely severe	Granulations still Grade 3; pannus greatly diminished; left hospital without permission
684	R. granular Grade 3	Pannus Grade 3	3		Very severe	Improved; 70% pannus; 30% granules; left at own request
684	L. granular Grade 3	Pannus Grade 3	3	7	Very severe	Improved; 70% pannus; 30% granules; left at own request
Outpatient	R. granular Grade 4	Pannus Grade 4	1	8	Very severe	Improved 30%; left hospital at own request
Outpatient	R. granular Grade 4	Pannus Grade 4	1	8	Very severe	Improved 30%; left hospital at own request
Outpatient	R. granular Grade 2	Pannus Grade 3	2	7	Moderate	Improved 30%
714	R. granular Grade 4	Pannus Grade 3	2	6	Moderate	Improved 30%; left hospital without permission
714	L. granular Grade 4	Pannus Grade 3	2	6	Moderate	Improved 30%; left hospital without permission

dibucaine hydrochloride. Of this solution (containing 0.25 gm. of chloramphenicol), 0.5 cc. was injected subconjunctivally into the upper fornix of each affected eye. If, after a few hours, a painful reaction ensued (which was usual), a saline wash was given and hot compresses were applied twice or thrice daily. In addition, atropine sulfate and 1% chloramphenicol were applied in ointment form. Also, sedatives were administered by mouth. When the reaction had subsided, usually in three to six days, another injection was given. Treatment was thus continued until clinical arrest of the disease had occurred or until the patient requested permission to leave hospital.

Results

Forty (80%) of the 50 eyes treated showed some improvement and in 22 this was considered to be spectacular (Table). Of those showing spectacular improvement, the average number of days between starting treatment and clinical arrest of the disease (disappearance of symptoms such as granules on the lids and edema of the cornea) was 13 days. The shortest time was 9 days, and the longest, 21 days. Shortness of time required to effect a clinical arrest of the disease is of great benefit to the average villager and a great saving of expense in treatment.

Summary of Data—Continued

Case No.	State on Admission		Injections, No.	Duration of Treatment, Days	Nature of Reaction	Result
	Lids	Cornea				
717	R. granular Grade 4	Pannus Grade 4	6	17	Moderate	Greatly improved
717	L. granular Grade 4	Pannus Grade 4	6	17	Moderate	Greatly improved
819	R. granular Grade 3	Pannus Grade 3	3	17	Moderate	Improved 30%; left at own request
819	L. granular Grade 3	Pannus Grade 3	3	7	Moderate	Improved 30%; left at own request
827	R. granular Grade 3	Pannus Grade 3	2	7	Severe	Improved 30%; left at own request
827	L. granular Grade 3	Pannus Grade 3	2	7	Severe	Improved 30%; left at own request
830	R. granular Grade 4	Pannus Grade 4	4	11	Severe	Greatly improved
830	L. granular Grade 4	Pannus Grade 4	4	11	Severe	Greatly improved
Outpatient	R. granular Grade 4	Pannus Grade 4	2	10	Extremely severe	Greatly improved
Outpatient	L. granular Grade 4	Pannus Grade 4	2	10	Extremely severe	Greatly improved
878	R. granular Grade 3	Pannus Grade 3	3	13	Moderate	Greatly improved
878	L. granular Grade 3	Pannus Grade 3	3	13	Moderate	Greatly improved
918	R. granular Grade 3	Pannus Grade 4	1	1	Severe	Left hospital without permission
918	L. granular Grade 3	Pannus Grade 4	1	1	Severe	Left hospital without permission
930	R. granular Grade 3	Pannus Grade 3	2	9	Severe	Greatly improved
Outpatient	R. granular Grade 2	Pannus Grade 2	1	1	Severe	Left hospital without permission
Outpatient	L. granular Grade 2	Pannus Grade 2	1	1	Severe	Left hospital without permission
936	R. granular Grade 3	Pannus Grade 3	4	14	Moderate	Greatly improved; smooth lids; pannus Grade 2
937	R. granular Grade 4	Pannus Grade 4	3	11	Moderate	Greatly improved; smooth lids; pannus Grade 2
937	L. granular Grade 4	Pannus Grade 4	3	11	Moderate	Greatly improved; smooth lids; pannus Grade 2
891	R. granular Grade 4	Pannus Grade 4	2	13	Moderate	Greatly improved; granules nearly smooth; pannus Grade 2
891	L. granular Grade 4	Pannus Grade 4	2	13	Moderate	Greatly improved; granules nearly smooth; pannus Grade 2
986	R. granular Grade 3	Pannus Grade 3	3	9	Slight	Greatly improved; smooth lids; pannus Grade 3
986	L. granular Grade 3	Pannus Grade 3	3	9	Slight	Greatly improved; smooth lids; pannus Grade 3

Effect on the Granules.—Where, before treatment, the lids were lined with thick bright-red juicy granules causing very severe photophobia and lacrimation, after treatment the lids had become pink and smooth and the patients could open their eyes without difficulty and without lacrimation. Without having seen it, it would have been difficult to believe that this effect could be achieved in such a short time and with so few injections.

Effect on the Pannus.—No treatment can cause vessels which have already formed in the cornea to disappear, but the injections diminished or cleared the cloudiness and edema of the cornea and transformed red photophobic eyes into white eyes reacting normally to light.

Follow-Up.—Owing to the economic situation of the average poor villager treated, who only with great difficulty is able to leave his home for a period of treatment, it is quite clear that none could return for reexamination. All that can be said is that at the end of treatment it appeared that the activity of the disease had been arrested completely.

Side-Effects.—A total of 144 injections were administered. Of 27 patients, 1 had only a slight reaction from the injection, 9 had a moderately severe reaction, and 17 had a severe or extremely severe reaction. These reactions consisted in chemosis of the bulbar conjunctiva, edema of the lids, pain, redness, photophobia, and lacrimation. The reactions persisted for one to six days. During this time, sedatives and hot compresses were administered and chloramphenicol 1% ointment was applied twice daily.

The interesting fact which emerged from treating those with severe reactions was not that some of the patients gave up the treatment and left the hospital but that, in spite of reactions, the improvement was so evident to most of the patients (after each reaction had subsided) that they thought it well worth while to continue. Of 27 patients, 9 left the hospital without permission and the rest continued with treatment.

Summary and Conclusions

A series of 50 eyes in 27 patients were treated by subconjunctival injections of chloramphenicol, with use of the standard vials supplied for intramuscular injection.

In 80% of the eyes there was some improvement, and in 44% of these improvement was spectacular.

The injections caused the disappearance of granules from the lids and edema from the cornea, and eyes previously angry and red in appearance became comfortable and white.

The injections produced local tissue reactions associated with pain, photophobia, and lacrimation. In 33.3% of patients this reaction was moderately severe, and in 63% of the patients it was severe or extremely severe. In spite of the severity of these reactions, 66.6% of the patients felt improved to such an extent that they persisted with the treatment.

Duration of this treatment was short and cost was low in comparison with other forms of treatment.

It is evident that chloramphenicol is a powerful agent against the causative organism of trachoma. With the production of an injectable form which does not cause reactions, the method of treatment outlined above should prove an excellent method of treating trachoma in all its active stages.

Dr. Eugene H. Payne, of Clinical Investigation, Parke, Davis & Company, supplied the Chloromycetin used in the investigations, and Sisters E. G. Stocken and K. Weatherhead and Mr. J. R. Coates provided the nursing care and observation under which the patients in this series were treated.

C. M. S. Hospital.

CORRECTION

Through error, the name of Dr. Albert P. Ley was omitted from the announcement in the September issue of the ARCHIVES of the award of the $250.00 prize by the Section on Ophthalmology of the American Medical Association to Dr. T. E. Sanders and Dr. Albert P. Ley for their paper entitled "Fungus Keratitis." This award was made at the Section Meeting in Chicago in June, 1956.

Vascular Changes in Eyes of Diabetic Rats

Alterations in the Anterior Segment

RALPH G. JANES, Ph.D., and PHILIP P. ELLIS, M.D., Iowa City

In 1952 Janes, Bounds, and Leinfelder [1,2] reported on cataract formation in alloxan-diabetic rats. At that time these authors observed intraocular hemorrhages in the form of hyphemas (with subsequent corneal vascularization) to have occurred in some of their animals.

These studies have been continued, and to date 30 rats have been noted to have developed hyphemas with subsequent corneal changes. The animals have been killed at various times after the development of these complications. Studies of the ocular vascular system have been made following intravascular injections of neoprene latex * or India ink. This paper describes the gross and histological changes observed.

Technique

Long-Evans strain adult male rats were fasted for 48 hours and then given a subcutaneous injection of 115 mg. of alloxan per kilogram of body weight. As previously, these rats were followed with regard to blood sugar levels, urine volumes, food intake, and body weight. Feedings consisted of Rockland rat ration or a synthetic diet complete with all essential food substances. In certain instances the diets were altered, and these instances have been indicated.

Periodic examinations were made with direct light, ophthalmoscope, and slit-lamp to observe development of cataract, presence of hyphema, and corneal vascularization.

The method of the vascular injection was as follows: 15 to 20 minutes before the animals were killed 150 U. S. P. units of heparin sodium were administered intraperitoneally. Under ether anesthesia the abdominal cavity and lower part of the thoracic cavity were exposed. The descending aorta was isolated, and a glass cannula was inserted into it. The animal was allowed to bleed to death through the cannula. Then the animal was injected with pigmented neoprene latex or India ink suspended in 5% reconstituted lyophilized human plasma, according to the technique described by Janes and Bounds.[3] After the injection the vessel was tied off and the rat was placed in a fresh solution of 10% formaldehyde for 24 hours. The eyes were then enucleated and opened coronally near the ora serrata. The anterior segment of the eye was bleached in the usual manner with 3% potassium permanganate and 2% oxalic acid. After washing, the iris and ciliary body were separated from the other structures. The whole cornea and iris were mounted flat in glycerin jelly. Other eyes were embedded in paraffin and sectioned. Hematoxylin and eosin, Masson's, and allochrome stains were used. Usually one eye of a particular animal was sectioned and parts of the other eye were prepared as whole mounts.

Observations

A. Gross Examination.—Corneal vascularization is rarely encountered in the normal members of our colony of rats. The chronic diabetic animals, on the other hand, do show some tendency toward corneal vas-

Received for publication July 23, 1956.

This work was supported in part by Grant B-237, U. S. Public Health Service.

From the Departments of Anatomy and Ophthalmology, College of Medicine, State University of Iowa.

* Supplied by E. I. du Pont de Nemours & Company, Inc., Wilmington, Del.

Relation of Hyphema to the Diabetic State, Cataract Formation, and Corneal Vascularization

Rat No.	Approximate Duration of Diabetes, Mo.	Blood Sugar, Av. Mg./100 Cc.	Length of Time with Mature Cataract, Wk.	Length of time with Hyphema	Corneal Involvement*
421	4	384	6	1 wk.	O.D. mild vascularization
				------	O.S. normal arcade
157	5 (on high-cysteine diet)	490	6	1 wk.	O.D. mild vascularization
				------	O.S. normal arcade
156	5	588	10	------	O.D. normal arcade
				9 wk.	O.S. moderate vascularization
174	5 (on high-cysteine diet)	440	5	2 days	O.D. dense vascularization
				3 wk.	O.S. dense vascularization
175	5	425	4	2 days	O.D. mild vascularization
				------	O.S. normal arcade
441	5 (high-potassium low-sodium diet)	390	5	------	O.D. normal arcade
				2 days	O.S. mild vascularization
424	6	508	9	4 wk.	O.D. dense vascularization
				------	O.S. normal arcade
246	6 (on animal fat diet part time)	460	7	3 wk.	O.D. moderate vascularization
				1 wk.	O.S. lost
272	6	325	8	3½ wk.	O.D. mild vascularization
				------	O.S. mild vascularization
316	7 (isoflurophate for 6 mo.)	402	12	7 wk.	O.D. moderate vascularization
				------	O.S. moderate vascularization
435	7	327	18	8 wk.	O.D. moderate vascularization
				------	O.S. normal arcade
436	7	584	14	------	O.D. moderate vascularization
				6 wk.	O.S. dense vascularization
331	8½ (on veg. fat diet part time)	597	12	7 wk.	O.D. moderate vascularization
				1 wk.	O.S. dense vascularization
336	9	459	20	4 wk.	O.D. moderate vascularization
				------	O.S. normal arcade
416	10 (on galactose part time)	303	9	8½ wk.	O.D. dense vascularization
				4 wk.	O.S. moderate vascularization
332	11	364	24	11 wk.	O.D. moderate vascularization
				------	O.S. normal arcade
425	15	236	21	2½ wk.	O.D. moderate vascularization
				------	O.S. normal arcade

* Degrees of vascularization: mild, 0-1/3 ingrowth toward pupillary margin; moderate, 1/3-2/3 ingrowth toward pupillary margin; dense, 2/3 ingrowth toward pupillary margin to complete vascularization.

cularization, but such vascularization is usually not very extensive. In the diabetic animals reported in the present study, four eyes, one from each of four animals, had corneal vascularization before there was any evidence of hyphema. In general, however, hyphemas preceded the corneal pathology.

Furthermore, in all the rats in this series mature cataracts preceded the development of spontaneous hyphemas. The interval of time between the appearance of these mature cataracts and hyphemas varied from 4 weeks to 19 weeks (Table). Usually the rapidity of development of the cataracts and the hyphema paralleled the severity of the diabetes, as judged by the blood sugar levels. Preceding the hyphemas dilated iris vessels were observed in some of the rats. There appeared also to be some correlation between the severity of the hyphema, the length of time the hyphema was present, and the degree of corneal vascularization. In one instance, an animal was killed two days after the initial appearance of a hyphema. Even at this time there was a marked dilation of corneoscleral veins and the beginning proliferation of marginal corneal vessels (Fig. 2). The other eye of this animal, which showed no evidence of hemorrhage in the anterior chamber, had a normal cornea (Fig. 1). When the hemorrhage was mild but of longer duration, the corneal vascularization was not so extensive (Fig. 3). On the other hand, when the hyphema was very severe complete corneal vascularization occurred in one week (Fig. 4). Many of the hyphemas increased the pressure in the eyes to the point where the anterior segment actually bulged forward. Because of this glaucoma, the cornea ruptured in two of the rats. None of the hyphemas showed a tendency toward clot formation, and it was possible in certain instances to see a red blood cell layer in the lower part of the eye and clear aqueous above.

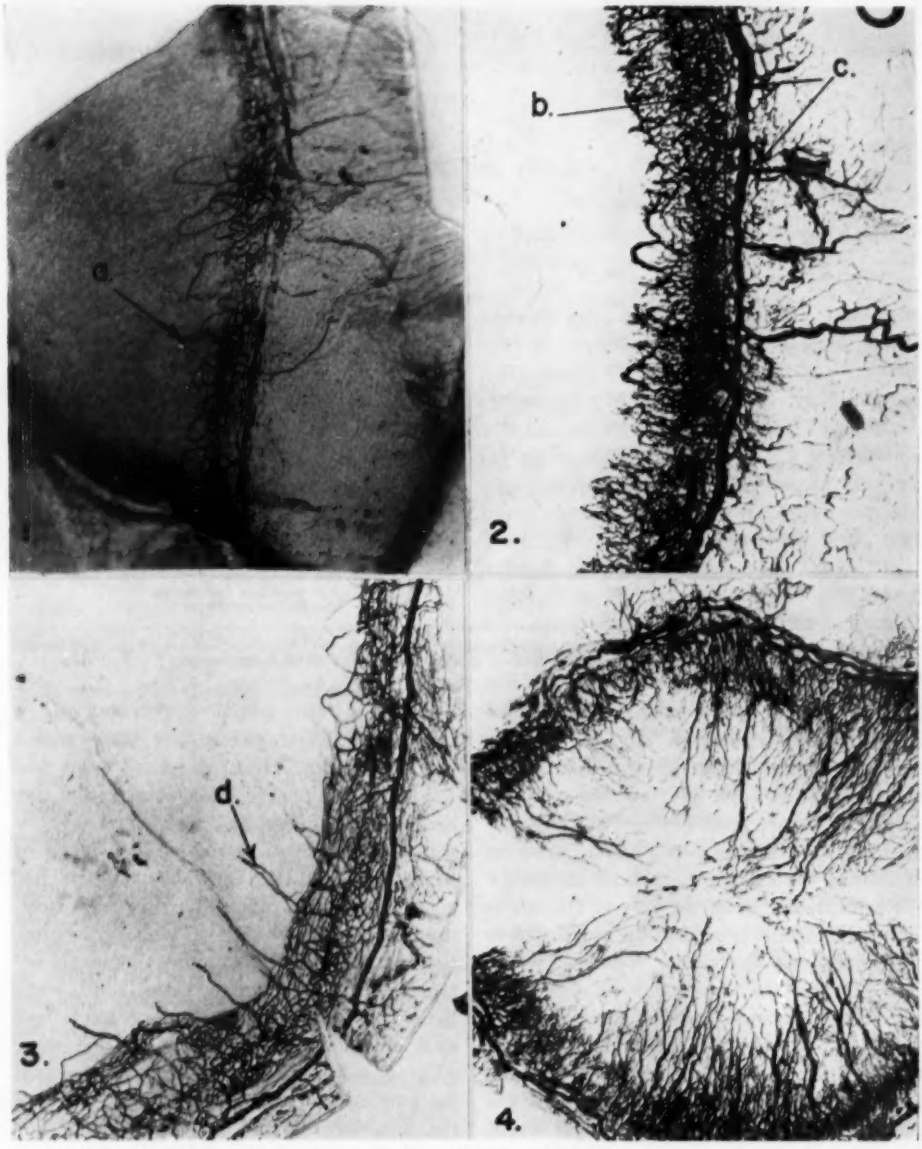


Plate I.—Whole mounts of corneas from diabetic animals.

Fig. 1 (Rat 441).—O. D. Normal limbal arcade with few loops extending into cornea; (*a*) the arcade.

Fig. 2 (Rat 441).—O. S. Limbal arcade very dense, with some proliferation. Corneoscleral vein greatly engorged. (*b*) Proliferation of vessels; (*c*) corneoscleral vein.

Fig. 3 (Rat 416).—O. S. Proliferation of marginal vessels with some capillaries growing into cornea; (*d*) capillary in cornea.

Fig. 4 (Rat 331).—O. S. Complete corneal vascularization with dilated corneoscleral veins.

Secondary pupillary membranes were seen as hyphemas regressed (Fig. 7). However, in most preparations this membrane was destroyed because of adhesions to the lens, the latter being removed during the preparation of the material.

B. Histologic Studies.—The histological studies were made on whole mount preparations as well as on sectioned material. In the flat preparations vascularization of the cornea began in the form of fine capillary twigs extending toward the center of the cornea from the limbal arcade (Figs. 2 and 3). The degree of vascularization was advanced in some corneas to the point where the entire cornea was covered (Fig. 4). In some instances it was possible to trace a capillary running from an arteriole on one side of the limbus to a vessel on the opposite side. The amount of corneal vascularization of the various eyes studied is shown in the Table.

The iris vessels appeared to be engorged in most of the whole mounts (Figs. 6 and 7). In three eyes there appeared to be aneurysmal dilations near the major circle

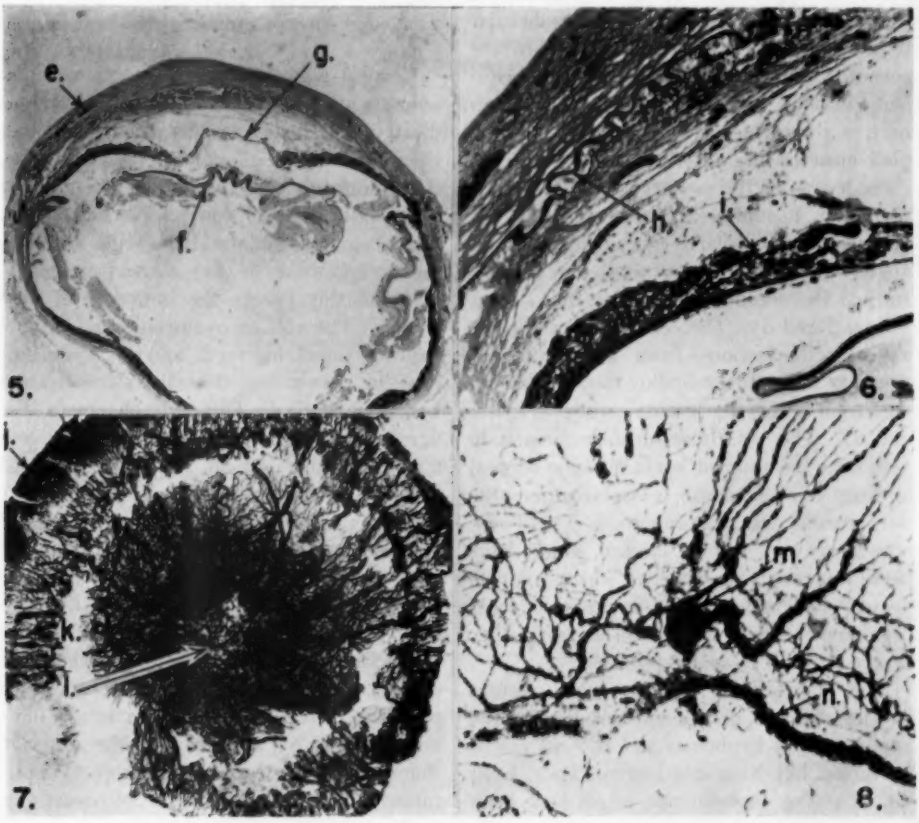


Plate II.—All animals with chronic diabetes.

Fig. 5 (Rat 174).—O. S. Medial sagittal section. Vascularization of cornea; secondary pupillary membrane; absorbing hyphema; engorged iris vessels. (*e*) Corneal vessel; (*f*) lens capsule; (*g*) secondary pupillary membrane.

Fig. 6.—Same as Figure 5, but high-power view of left side of anterior chamber and associated structures to show more detail. (*h*) Descemet's membrane; (*i*) iris.

Fig. 7 (Rat 331).—O. S. Whole mount of iris, showing engorged iris vessels and secondary pupillary membrane. (*j*) Choriocapillaris; (*k*) ciliary body; (*l*) secondary pupillary membrane.

Fig. 8 (Rat 416).—O. D. High-power view of iris, showing aneurysmal dilatation. (*m*) Major arterial circle; (*n*) aneurysmal dilatation.

(Fig. 8). Although undoubtedly this was caused by the pressure of the fluid which was being injected, it did indicate that the walls of these vessels were weakened as the result of the disease. Additional evidence that the walls of certain blood vessels were weakened was the fact that the injected medium was often found in the anterior chamber even though previously there had been no hemorrhage. As far as could be ascertained, there was no neovascularization of the iris proper.

The sectioned eyes showed various degrees of hyphemas. There was blood on the surface of the iris in the trabecular tissue and on the posterior surface of the cornea. Blood was found in the vitreous body in only two rats. Fine vascular connective tissue membranes frequently occupied most of the anterior chamber. These extended from the posterior surface of the cornea to the anterior surface of the iris and were particularly dense in the iris angle. Extensions from those on the iris formed the secondary pupillary membranes (Figs. 5 and 6). The corneas showed variable vascularization—from a few vessels growing in from the limbus to dense vascularization across the entire cornea (Figs. 5 and 6). The vessels were more frequently seen near the anterior surface of the corneal stroma, but in dense vascularization the deep stroma was also involved. These vessels were very minute, and it would have been impossible to identify them as true vessels had not India ink been injected previously. The endothelium showed rather severe damage in many sections.

The question of whether other factors besides diabetes per se might influence the appearance of hyphemas and corneal vascularization has been considered. Data from the following experiments, which have been carried out in this laboratory during the past few years, have been examined: (1) animals given a diet in which the sole source of fat was lard; (2) animals fed fat from vegetable oils; (3) animals given 60% of their carbohydrate as galactose; (4) animals given subcutaneous injections of 40 mg. of cysteine twice daily; (5) a series of rats receiving a high-potassium low-sodium diet for two months, and, finally (6), a group of animals which were given isoflurophate (DFP) topically applied to the eyes once a day for six months. Except for one of the experiments there appeared to be no increase or decrease of hyphemas or corneal vascularization during these studies, in comparison with control diabetic animals. However, the rats treated with isoflurophate seemed to be more prone to corneal vascularization, but not to hyphemas.

Comment

Corneal vascularization in experimental animals has been observed to follow various dietary deficiencies, trauma, edema, and biochemical alterations of the corneal tissue. According to Cogan,[4] edema is essential for the development of corneal vascularization. This theory postulates that, with swelling, the compactness of the corneal tissues is lost and this favors the ingrowth of new vessels. The role of hyaluronic acid in preventing vessel ingrowth and of hyaluronidase in preventing corneal vascularization has been studied. Different observers disagree as to its importance.[5,6] Ashton and Cook[7] summarized all theories of corneal vascularization into two main groups: (1) a process combining growth stimulation and positive chemotaxis and (2) destruction of growth-inhibiting substances or compactness of tissue. Their experiments led them to believe that corneal compactness was the main factor in prevention of development of vascularization. Langham[8] was able to produce corneal vascularization in six days by injection of alloxan into the anterior chamber of rabbits and also by topical application to the cornea. He did not report any hyphemas.

In the present study two conditions would have favored alteration of the stromal compactness: (1) changes in the stromal fibers because of the diabetes and (2) damage to the cornea from glaucoma secondary to the hyphema.

It is felt that the hyphemas developed from ruptured iris vessels, even though it was impossible to find such vessels in histological preparations.

Summary

Anterior segment hemorrhages and corneal vascularization have been observed to occur frequently in rats with severe chronic diabetes. Studies of the vascular system in the rat's eye have been made following intra-arterial injection of India ink or neoprene latex. The studies indicate that the iris blood vessels usually become engorged, dilate, and finally burst. The resultant hyphema and probable glaucoma interfere with the corneal metabolism sufficiently to allow ingrowth of new vessels. Posterior segment hemorrhages in the diabetic rat are rare. The vascular changes may be correlated with the severity of the diabetes rather than with the duration of the disease.

Department of Anatomy, State University of Iowa.

REFERENCES

1. Janes, R. G.; Bounds, G. W., Jr., and Leinfelder, P. J.: Ocular Complications in the Rat Made Diabetic with Alloxan, A. M. A. Arch. Ophth. 48:414 (Oct.) 1952.

2. Bounds, G. W., Jr.; Janes, R. G., and Leinfelder, P. J.: Cataracts Induced by Alloxan Diabetes in Rats and Rabbits: Experimental Studies, A. M. A. Arch. Ophth. 54:564 (Oct.) 1955.

3. Janes, R. G., and Bounds, G. W.: The Blood Vessels of the Rat's Eye, Am. J. Anat. 96:357 (May) 1955.

4. Cogan, D. G.: Vascularization of the Cornea: Its Experimental Induction by Small Lesions and a New Theory of Its Pathogenesis, Arch. Ophth. 41:406 (April) 1949.

5. Meyer, K., and Chaffee, E.: The Mucopolysaccharide Acid and Its Enzymatic Hydrolysis, Am. J. Ophth. 23:1320 (Dec.) 1940.

6. Woodin, A. M.: Hyaluronidase as Spreading Factor in the Cornea, Brit. J. Ophth. 34:375 (July) 1950.

7. Ashton, N., and Cook, C.: Mechanism of Corneal Vascularization, Brit. J. Ophth. 37:193 (April) 1953.

8. Langham, M.: Observation of Growth of Blood Vessels into the Cornea: Application of a New Experimental Technique, Brit. J. Ophth. 37:210 (April) 1953.

The Effects of Nutritional and Endocrine Factors on an Inherited Retinal Degeneration in the Mouse

D. R. LUCAS, M.D., and J. P. NEWHOUSE, B.Sc., London, England

Introduction

In 1951, Brückner described a strain of albino mouse in which the outer nuclear layer of the retina was absent, thus resembling the classical "rodless" strain of Keeler (1924, 1926). Both conditions show a simple recessive mode of inheritance and have been compared with human retinitis pigmentosa. Sorsby, Koller, Attfield, Davey, and Lucas (1954) and Tansley (1954) reported that in Brückner's strain the degeneration of the outer nuclear layer began at about 11 days after birth, while differentiation of the retina was still in progress. Tansley (1934, 1936) had earlier discovered that among normal rats a maternal diet containing not more than 2γ β-carotene per day affected the retinae of the sucklings. Growth of the outer limbs of the rods was retarded, and thinning occurred at the junction of the outer and inner limbs. Johnson (1939, 1943) showed that, in young rats fed on a diet highly deficient in vitamin A, the degeneration slowly spread to the other retinal layers until its effects had become irreversible by treatment with vitamin A. In view of these findings, Karli (1952) tested the effects in litters of the Brückner strain of a maternal diet rich in fat-soluble vitamins on the development of the retinal lesion during gestation and lactation, but without success. Since the diet only of the mother was supplemented in this work, it had to be assumed that any additive intended for the litter would be adequately secreted in the milk.

Received for publication June 18, 1956.

Wernher Group for Research in Ophthalmological Genetics, Medical Research Council, Royal College of Surgeons of England.

Nutritional control has occasionally proved successful in treating diseases with clearly defined hereditary features. Thus, restriction of certain constituents of diet in order to limit the accumulation of their unmetabolized intermediates has given favorable results in phenylketonuria, diabetes mellitus, and Niemann-Pick disease. In discussing the roles of heredity and environment in the dystrophies with cataract, Buschke (1943) pointed out that many enzyme reactions depend on two main components: the apoenzyme, which is probably genotypically determined, and the coenzyme, usually of dietetic origin. Either might fail with similar results upon some important metabolic process in the tissues concerned. He illustrated his concept by reference to the relations between pernicious anemia and tropical sprue and exogenous and endogenous rickets.

The object of the present work was to test the possibility that retinal degeneration in the mouseling could be influenced by the administration of a wide range of agents of biochemical importance before and during its development. Since the retinal lesion might follow the breakdown of some important enzymatic process, various coenzymes, vitamins, and intermediates of carbohydrate metabolism were included among the substances tested; many amino acids and several hormones were also tried. Nerve cells are notably selective in their absorption of substances from the extracellular fluid, and large quantities of the chemicals under test were therefore administered in order (1) to correct any possible dietary deficiency and (2) to provide high tissue fluid concentrations favorable to their penetration

into the retina. Substances were administered not only to suckling mice but also to their mothers, by parenteral or oral routes. An investigation of the effects of undernutrition upon the developing retina was also made.

Methods

Animals.—All work was performed on an inbred colony of mice of the Brückner strain. Two or more litters, each numbering 5 to 8 members, were used to test the effects of each substance. The adults received water and rat cake (with or without supplement) ad libitum, consumption being noted daily. Diet 41, the cubed rat cake in use (Associated London Flour Millers, Ltd.), is reported to contain 13.7% protein, 3.5% fat, 49.0% soluble carbohydrate, and 1.5% fiber (Bruce and Parkes, 1949).

For histological examination, one or two animals from each litter were killed at 11 days, an age when the lesion is just noticeable and any advance in normal onset most conspicuous. Since the tempo of the process is beginning to slow down at 17 days, the rest of the animals were usually examined at this age, so that any transitory delay would more readily be demonstrated. Some substances were studied in more detail by examining the animals at intermediate times.

Treatment.—Substances to be tested were given either orally (to the mother) or subcutaneously (to both mother and litter).

(1) Oral: Since litters are not weaned before three weeks, direct feeding of many substances is impracticable. The diet of some mothers was therefore supplemented throughout pregnancy and lactation with various test substances to the greatest extent consistent with good health and attention to their litters. The degree to which these additives reached the offspring was naturally variable, but supplementation was primarily intended to correct any possible nutritional deficiency.

The substances given orally, admixed with Diet 41, to adult females from mating until 17 days post partum are listed in Table 1. The proportion adopted of each additive, except perhaps of lecithin and the vitamins, was about the maximum tolerated. Animals were entirely dependent on the supplemented diet, consumption being little different from that of control animals on Diet 41 without additives. Maternal uptake of a supplement at any time can be approximately computed from the following data for the mean daily consumption (in grams) of Diet 41 in 24 control animals at various periods before and after the birth of 26 litters comprising from five to eight offspring each (days before and after birth are indicated by minus and plus signs, respectively): 3.5 gm. (−21); 4.0 gm. (−14); 4.1 gm. (−7); 5.5 gm. (−2); 4.6 gm. (0); 6.2 gm. (+2); 9.9 gm. (+7); 10.6 gm. (+10); 12.5 gm. (+14); 11.7 gm. (+16).

The rat cake diet of three pairs of mothers was supplemented throughout gestation and lactation by 0.1%, 0.2%, or 0.4% (w/w) of *n*-propylthiouracil. The resultant offspring, numbering 18 in all, were killed at 12, 13, 14, or 17 days.

TABLE 1.—*Oral Dosage in Adult Female Mice During Gestation and Lactation*

Substance	Quantity Added to Rat Cake, Gm./100 Gm.	Typical Maternal Consumption, Gm.		
		During Gestation	During Lactation	Total
Casein, light white soluble	15.0	14	30	44
Starch, wheat	67.0	33	94	127
Arachis oil	20.0	17	41	58
Lecithin, egg (95%-100%)	5.0	5.0	8.3	13.3
Linoleic acid (linseed oil fatty acids)	5.0	1.2	6.7	7.9
Marmite (yeast extract)	20.0	15	42	57
Nucleinic acid B. P. C. 1934	10.0	10	23	33
Folic acid	0.05	0.005	0.090	0.095
L-Methionine	10.0	12	21	33
L-Cystine	5.0	5	7	12
L-Cysteine hydrochloride	5.0	7	12	19
L-Glutamic acid	15.0	14	32	46
Sodium L-glutamate monohydrate	15.0	15	38	53
n-Propylthiouracil	0.1-0.4	0.09-0.36	0.17-0.68	0.26-1.04

TABLE 2.—*Subcutaneous Dosage in Adult Female Mice and Their Litters During Gestation and Lactation*

Substance	Dosage (Mg./Day) in Adults During Gestation and Lactation	Dosage (Mg.) in Litters on Selected Days After Birth				Remarks
		2	10	16	Total	
Vitamin A alcohol in Arachis oil	--	250	1,500	5,000	14,800	Dosage in i.u.
Thiamine hydrochloride	40	0.50	1.13	1.50	14.0	
Riboflavin	1.0	0.05	0.25	0.45	2.30	
Nicotinamide	30	1.0	3.0	5.0	33.5	
Pyridoxine hydrochloride	12.5	0.75	2.50	3.0	28	
Pantothenyl alcohol (Panthenol)	12.5	2.0	7.0	13	83	
D-Biotin	2.5	0.08	1.00	1.30	8.9	
p-Aminobenzoic acid, sodium salt	25	1.5	8.0	9.5	72	
Inositol (meso)	100	3.0	15	22	135	
Choline chloride	--	0.10	0.65	1.20	7.3	Poorly tolerated
Vitamin B_{12}	0.050	0.004	0.025	0.040	0.290	
Vitamin B preparation (Becozym)	0.50	0.04	0.15	0.20	1.58	Dosage in ml.
Liver preparation (Anahaemin)	0.40	0.03	0.10	0.16	1.22	Dosage in ml.
L-Ascorbic acid	70	2.5	10.0	35.0	163	
Disodium DL-α-tocopheryl phosphate	10	0.8	2.4	3.0	21.6	Poorly tolerated
Aminoacetic acid	50	3.0	7.0	12.5	88	
DL-α-Alanine	50	1.0	7.0	13.0	82	
L-Serine	50	1.5	10.0	18.0	120	
L-Arginine monohydrochloride	50	3.0	16.0	24.0	161	
L-Histidine monohydrochloride monohydrate	50	1.0	5.0	8.0	63	
DL-β-Phenylalanine, sodium salt, suspension	25	0.3	6.0	12.5	58	Poorly tolerated
DL-Tryptophan, suspension	25	0.6	4.5	6.0	42	
L-Proline	25	1.0	15.0	15.0	130	
L-Methionine	20	0.4	1.8	3.0	22	
L-Cysteine hydrochloride	20	0.4	3.6	4.8	34	Poorly tolerated
Dimercaprol (in Arachis oil)	1.5	0.05	0.10	0.15	1.15	Poorly tolerated
Sodium lactate	100	2.0	20.0	25.0	165	
Sodium pyruvate	50	3.0	8.0	12.5	130	
Sodium fumarate	100	3.0	7.0	11.0	97	
Sodium citrate (trisodium dihydrate)	25	1.5	7.0	11.0	70	
Sodium succinate hexahydrate	25	2.0	20.0	25.0	182	
Sodium α-ketoglutarate	25	1.5	9.0	18.0	100	
Sodium oxaloacetate	25	1.5	6.0	12.5	75	
Sodium aconitate	--	1.0	6.0	5.0	58	Dosage as free acid
Sodium hydrogen malate	50	1.5	5.0	12.5	75	
Nucleic acid, sodium salt from yeast	24	1.4	4.8	7.2	80	
Nucleic acid, sodium salt from thymus	25	1.5	5.5	10.0	63	
2,4-Dinitrophenol, sodium salt	--	0.030	0.083	0.060	0.615	
Glutathione	10	0.3	4.2	6.6	43.6	Given daily in 2 parts
Adenosine 5'-triphosphoric acid, sodium salt	--	0.10	1.20	3.60	16.4	Given daily in 2 parts
Hexose 1,6-diphosphate, calcium salt (85%)	--	0.10	1.50	4.50	17.0	Given daily in 2 parts
Cytochrome c	--	0.08	1.00	1.40	9.8	Given daily in 2 parts
Diphosphopyridine nucleotide (95%)	--	0.04	0.24	0.40	3.56	Given daily in 2 parts, with vitamin A and nicotinamide

At an early stage in this work it was noted that the characteristic development of the lesion was somewhat retarded, though not halted, in certain treated animals that were much underweight. It was found possible to produce seven underweight litters by limiting the maternal daily intake of rat cake during pregnancy and lactation to about two-thirds of the mean consumption of a control group of 10 mothers who had brought up their litters satisfactorily on an unlimited rat cake diet; the uptake of the

TABLE 3.—*Further Substances Daily Given Subcutaneously to Suckling Mice*

Substance	Age During Treatment, Days	Typical Dose (Mg.) on Selected Days					Total Dose, Mg.
		2	6	10	13	16	
Thyroxin, sodium salt	2-11	0.0010	0.0015	0.0020	--	--	0.0180
Methylthiouracil	2-17	1.2	2.1	3.0	3.6	4.2	35
Anterior pituitary extract (Antuitrin) (dosage in rat units)	2-15	0.24	1.12	2.24	3.20	--	17.7
Epinephrine hydrochloride	2-17	0.004	0.012	0.020	0.026	0.030	0.210
Sodium L-glutamate	2-17	4	12	20	26	30	250
Sodium L-aspartate (dosage as free acid)	2-17	0.75	1.75	2.4	3.6	4.4	29
L-Glutamine	2-17	1.0	6.0	12.0	12.0	16.0	117
Mean body weight and standard deviation of 5 control litters each of 5 animals		1.81±0.14	2.99±0.45	4.42±0.41	5.29±0.55	5.88±0.47	

latter group was similar to that already cited.

These underfed animals varied in weight from 2.6 to 4.8 gm., at 17 days, thus overlapping the normal range; the average weight and standard deviation were 3.61± 0.68 gm., i. e., 69% of the mean value for the 19 histological controls (5.21±0.95 gm.).

(2) Parenteral: The aim of treatment here was to provide the litter with the maximum amount of supplement both before and after birth. Each substance listed in Tables 2 and 3 was therefore injected subcutaneously once daily to mouselings, usually from ages 2 to 16 days. Many of the substances in Table 2 were also given subcutaneously to mothers from the second week of pregnancy until birth of the litter and often until 17 days later. In a few preliminary trials, the maximum dosages consistent (1) with successful birth and care of the litter by the mother and (2) with normal postnatal growth and development in the litter itself were approximately determined. Thus litters, aged 2 days, were given an arbitrary dose of a test substance, which was increased daily with growing body weight. Where members of the litter died or began to lose weight, dosage (milligrams per gram of body weight) was reduced daily by successive quarters until a tolerated level had been reached. This dosage was adhered to in subsequent trials of the supplement. Tolerance to many substances appeared to increase with age, for overdosage was more common in litters aged 10 days or less than afterwards. With a few substances, e. g., biotin, a liver preparation (Anahaemin), and vitamin B_{12}, volume considerations made it impossible to attain the maximal tolerated dosage in the litters.

Substances were normally prepared in aqueous isotonic solution or suspension, buffered to pH 7.4, except vitamin A alcohol and dimercaprol (2,3-dimercaptopropanol), which were dissolved in Arachis oil. Some of the less readily soluble substances, e. g., biotin, methylthiouracil, tryptophan, β-phenylalanine, and p-aminobenzoic acid, were given as suspensions by solution in alkali and adjustment to pH 7.4 with phosphate buffer in the presence of a dispersing agent (sorethytan [20] monooleate [Tween 80]). The amino acids given were of the L (+) series, unless this isomer was not available. Concentrations were adjusted to give injection volumes of 0.2 to 1.0 ml. in adults and 0.02 to 0.40 ml. in the litters. The mean body weights and standard deviations of five control litters, each comprising five members, and typical doses given on several representative days are detailed in Tables 2 and 3.

Substances: Further particulars of some of the substances and the dosages given are as follows:

Becosym (Roche Products Ltd.): a vitamin B-complex preparation, containing (mg/ml.) thiamine hydrochloride 5, riboflavin 2, nicotinamide 20, pyridoxine hydrochloride 2.

Anahaemin (British Drug Houses Ltd.): an active erythropoietic fraction of liver.

Dimercaprol (injection solution BAL, Allen & Hanbury Ltd.): a solution in Arachis oil of 5% (w/v) or less.

Antuitrin (Parke, Davis & Co. Ltd.): an extract of the anterior pituitary gland, containing the growth hormone, 8 rat growth units per milliliter, was given only to litters. Half of each litter received from 2 days a basic dosage of 0.25 rat units per day, with a daily addition of 0.70 rat units per gram increase in body weight; the untreated members of each litter served as controls. There was little difference in rate of growth between the groups until the 8th day after birth; between 8 and 13 days the mean weight of experimental animals rose by 56%, that of controls by 34%.

Methylthiouracil: given only to litters in aqueous suspension buffered to pH 7.4 after solution in alkali. Half of each litter received 0.6 mg/gm. body weight per day, from 2 to 16 days, the others serving as controls. The mean body weight of experimental animals was 33% below the control value at 13 days and 14% below at 17 days.

2,4-Dinitrophenol, sodium salt: A daily dosage (litters only) of 0.015 mg/gm. body weight given to half of each litter caused the mean body weight of the test group to reach only 87% of the mean value for the untreated control group at 14 days. Animals were killed at 15 days.

Epinephrine (Adrenalin) Hydrochloride: A 0.1% (w/v) commercial preparation diluted by five times was used. The daily dosage (to litters only) was progressively raised from 0.0017 mg/gm. at 2 days to 0.0060 mg/gm. at 16 days.

L-Thyroxin, sodium salt: This substance was daily administered in aqueous solution to half the members of some 10 litters between the ages of 2 and 9 days, the untreated animals serving as controls. Dosage was usually 0.5γ/gm. body weight, but in four litters it was raised to 5.0γ/gm., with slightly more effect upon histological findings and fall in body weight. The effect of the higher dosage upon body weight was more difficult to reverse by suspension of treatment once a decline had begun. These findings are in accord with those of McEachern (1935), who reported that in rats any dosage between 2.5γ and 30γ/gm. per day would produce loss of weight, asthenia, and, ultimately, death. In the present work, 18 treated animals plus the untreated controls from the same litters were killed for histological examination at 11 days; the mean body weights and standard deviations for the two groups at this age were, respectively, 3.97±0.32 gm. and 4.77±0.95 gm. When treatment was begun at ages 2 to 3 days, the daily gain in weight of the experimental animals began to fall below that of the controls at 7 to 8 days after birth.

Sodium L-glutamate monohydrate: This substance was administered daily to some litters in quantities increasing by 1.5 to 2.0 mg. per day, according to tolerance; this scheme gives dosages of about 2.2, 4.0, 4.5, 5.0, and 5.0 mg/gm. body weight at ages 2, 6, 10, 13, and 16 days, respectively. Several mothers (weight before mating, 24 to 32 gm.) received 40 mg. sodium glutamate daily throughout pregnancy and lactation. The number of offspring involved when glutamate was given to mothers only was 14, to the litters only 19, and to both mothers and litters 41. The 53 survivors were killed at various ages between 5 and 17 days for histological examination (cf. Newhouse and Lucas, 1957).

Sodium L-aspartate: This substance was administered from birth to the mothers in quantities of 40 mg. per day and to the litters at dosages rising from 0.4 mg/gm. at 2 days to 0.8 mg/gm. at 16 days (dosages given as the free acid).

Histological Methods.—The eyes were fixed intact in acid Zenker's fluid, dehydrated through graded strengths of ethanol, and embedded in paraffin wax. In some cases the lenses were removed before embedding. Sections were cut through the globe in an anteroposterior plane and stained with Erhlich's hematoxylin and eosin Y.

Assessment of Results.—Assessment of the degree to which the timetable of development of this lesion had been altered was made on the basis of the number of rows of rod nuclei remaining in the outer nuclear layer and the amount of rod débris. Since the lesion develops more quickly in the area centralis, the number of nuclei was recorded both in this part of the retina and 0.5 mm. from the ora serrata. As the orientation of the globe and plane of section were not standardized accurately, the method is only semiquantitative.

Results

Untreated Litters.—To determine the extent to which the rate of progress of the degeneration varied in different animals, 19 affected animals (three litters) were killed at 17 days and the eyes examined histologically.

In all these animals there were one or two rows of rod nuclei centrally and two or three rows peripherally (Fig. 1); only traces of rod débris remained. The variation encountered was thus relatively small and did not appear sufficient to invalidate the proposed method of assessing the results of various treatments.

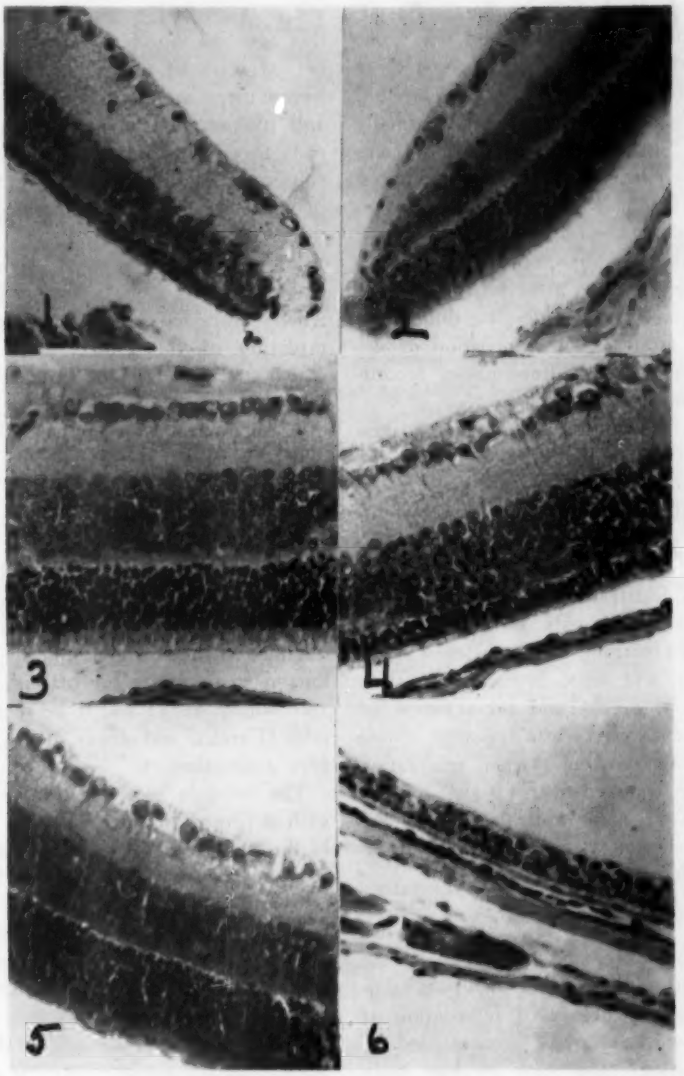


Fig. 1.—Peripheral retina of untreated mouse of 17 days showing almost total loss of the outer nuclear layer.

Fig. 2.—Peripheral retina of mouse of 17 days in undernutrition series, showing outer nuclear layer still intact.

Fig. 3.—Area centralis of untreated mouse of 11 days, showing outer nuclear layer intact, but pyknotic nuclei are evident.

Fig. 4.—Area centralis of thyroxine-treated mouse of 11 days, showing advanced dissolution of the outer nuclear layer.

Fig. 5.—Area centralis of propylthiouracil-treated mouse of 14 days, showing outer nuclear layer intact but a few pyknotic nuclei appearing.

Fig. 6.—Retina of mouse of 17 days treated with glutamate, showing almost total destruction of inner as well as outer layers.

The magnification is $\times 290$ in each Figure.

Litters of Underfed Mothers.—As already mentioned, it was noticed that some litters in which the mother received large doses of vitamin A were very underweight and the retinal lesion was less than normally advanced. Since the degeneration commences at a particular stage of differentiation, any factor retarding differentiation might also delay the onset of the lesion and thus the extent of dissolution of the outer nuclear layer 17 days after birth. The appearance would, in practice, be difficult to distinguish from a true retardation of degeneration in a retina differentiating according to the normal timetable.

A total of 17 animals was examined histologically from seven litters in which the mothers were underfed as described. More than normal preservation of the outer nuclear layer was noted in nine of these animals. The degree to which this occurred in some is illustrated in Figure 2. The remaining eight animals showed intermediate pictures merging into the normal range of variation, and some inverse correlation between body weight and preservation of the outer nuclear layer was apparent. None of the animals showing marked retardation of the lesion weighed over 4.0 gm., but, on the other hand, some animals of only 2.5 to 3.0 gm. showed a relatively small deviation from the normal range.

Treated Litters.—Thyroxin, thiouracil derivatives, glutamate, and aspartate are dealt with separately below. None of the litters treated with the other materials tabulated showed any degree of retardation of the lesion which was not accompanied by signs of malnutrition such as low body weight, e. g., litters treated with α-tocopheryl phosphate were very weak and underweight and tended to show the picture described above.

(1) Thyroxin: Histological examination of the eyes at 11 days showed that the retinal lesion was invariably more advanced in the thyroxin-treated animals. At 11 days there are normally eight or nine rows of immature rod nuclei, of which occasional ones show pyknosis. The rods themselves are at a normal stage of development for this age. In the treated animals, the number of rows of nuclei was reduced to between three and five in the area centralis and pyknotic nuclei were abundant. The rods themselves were also undergoing dissolution. The difference in a typical pair of treated and untreated littermates is illustrated in Figures 3 and 4.

Although the degree of advancement in not very great, it is perhaps more striking when contrasted with the tendency to retardation of the lesions seen in animals which are underweight because of undernutrition.

(2) Thiouracil Derivatives: The animals which received methylthiouracil, although slightly underweight compared with untreated littermates, did not show a significant degree of retardation of the lesion. There was, however, evidence that the material was not readily removed from the site of injection, and oral treatment of the mothers with *n*-propylthiouracil, which is known to penetrate the placenta (Peterson and Young, 1952) and to be secreted in the milk (Fazekas and others, 1951), was therefore undertaken.

The animals reared by mothers treated with *n*-propylthiouracil showed retardation of the lesion varying in degree and merging into the normal range. Figure 5 illustrates a 14-day-old treated animal in which the lesion is only just evident. This particular animal was considerably underweight. The 10 animals killed at 17 days averaged 4.13 gm. in weight, which is less than the control average weight of 5.21 gm. at this age but more than the average of 3.60 gm. in the undernutrition series. The findings in the *n*-propylthiouracil-treated animals were, in general, similar in degree to those of the undernutrition and other experiments in which there was failure to gain weight normally.

(3) Glutamate and Aspartate: When litters were treated with sodium L-glutamate according to the schedule given in Table 3, it was found that the inherited retinal lesion developed normally but, in addition, the

inner retinal layers underwent dissolution. Sodium glutamate also affects normal mice, both suckling and adult, in a similar way (Newhouse and Lucas, 1957). In the retinal dystrophy mice, as in normals, there is progressive destruction of the inner nuclear layer, ganglion cells, and both fiber layers during the course of injections. By 11 days, when the genetic lesion normally commences, the inner layers are already considerably damaged in glutamate-treated animals, and by 17 days the retina is represented by a thin layer of cells lying between its limiting membranes (Fig. 6).

Of the litter of four animals treated with sodium L-aspartate, two showed slight peripheral atrophy of the retina similar to the effect of aspartate on normal mice described elsewhere (Newhouse and Lucas, 1957). The genetic lesion was unaffected.

Glutamine neither damaged the retina nor affected the progress of the hereditary lesion.

Treatment of the mother alone with oral or parenteral glutamate neither affected the progress of the genetic lesion nor damaged the retina independently.

Comment

The substances administered in this work may be divided into six groups, namely: vitamins, intermediates of carbohydrate metabolism, amino acids (including certain sulfhydryl donors), hormones, and a miscellaneous group which included the gross nutritional constituents.

Some of the substances tested, including vitamin A, α-tocopheryl phosphate, nicotinamide, diphosphopyridine nucleotide, and hexose diphosphate, are believed to be concerned in rod metabolism, especially in the biosynthesis of retinene (Wald, 1953), but none influenced the progress of the lesion. Sodium iodacetate, a reputed inhibitor of sulfhdryl-dependent enzymes, induces visual cell necrosis in the rabbit (Noell, 1951); sulfhydryl donors, such as glutathione, cysteine, and dimercaprol did not, however, mitigate the hereditary dystrophy. Nor did substantial doses of various amino acids, apart from the sodium salts of glutamic and aspartic acids, influence the retina. While many of the substances tested are known to penetrate cerebral tissue, the possibility that some may fail to reach the visual cells of the retina in effective quantity cannot be excluded.

Three factors, namely, thyroxin, propylthiouracil, and undernutrition, affected the course of development of the lesion, but not its final outcome. Animals treated with thyroxin showed accelerated development, while those born and suckled by mothers treated with propylthiouracil or receiving a normal, but limited, dietary intake showed retarded development. Treatment with growth hormone, while causing increased bodily growth, did not advance the development of the lesion.

Thyroid and Growth.—When thyroxin is administered to frog tadpoles, the appearance of the corneal reflex is advanced (Kollros, 1943) and the rate of growth of sclera and retina is enhanced (Tusques, 1951). Hoskins (1927) has reported that regular treatment of normal newborn rats with acetyl thyroxin accelerates development of epiphyses, eyes, and skull without corresponding increase in body size. Conversely, both dimensional growth and tissue maturation in many mammalian species (sheep, dogs, cats, rabbits, rats) have been retarded by thyroidectomy soon after birth (e. g., Dye and Maughan, 1929; Todd, Wharton, and Todd, 1938). In newborn rats, this treatment resulted in cretinism and delayed opening of the eyes (Salmon, 1938, 1941; Scow and Simpson, 1945); hypothyroidism induced in similar animals by feeding the mothers with propylthiouracil had comparable effects, including developmental failure of the eyes (Fazekas, Graves, and Alman, 1951).

Evans and co-workers, in studying the influence of endocrine factors upon growth in young rats, concluded that increases in body weight, visceral weight, and skeletal dimensions were mainly promoted by the pituitary growth hormone, whereas thyroxin

was concerned with effecting maturation of skeleton, hair, and endocrine glands; the optimal balance between these characteristics was obtained by a combination of both hormones (Evans, Simpson, and Pencharz, 1939; Scow and Marx, 1945; Scow, Simpson, Asling, Li, and Evans, 1949; Ray, Simpson, Li, Asling, and Evans, 1950). At 60 days, the brains and eyeballs of rats thyroidectomized at birth were somewhat lighter than those of controls of the same age, but, in proportion to the diminished body weight, they were two to three times heavier than normal (Scow and Simpson, 1945; Scow and others, 1949). Administration of growth hormone between 30 and 60 days did little to correct the retardation of these organs; only when thyroxin was given did the eyeball become round and the head assume its normal size and pointed outline (Ray and others, 1950). Nor did hypophysectomy at 6 or 28 days delay opening of the eyes or depress the weights of brain or eye, which are normally almost fully grown by four weeks (Walker, Simpson, Asling, and Evans, 1950; Asling, Walker, Simpson, Li, and Evans, 1950; Walker, Asling, Simpson, Li, and Evans, 1952). Though the thyroid develops its characteristic structure in rats only three days before birth (Kull, 1926), its importance to the development of the eye during the ensuing month is considerable.

Eayrs and Taylor (1951), who produced hypothyroidism in rats by daily treatment from birth with methylthiouracil, obtained somewhat similar results. Both pyramidal-cell development and the appearance of certain motor reflexes were delayed in these animals. Before 15 days growth of brain was more retarded than body growth, but between 15 and 24 days brain developed at a normal rate, whereas somatic growth rate was depressed. Since only the latter effect is reversed by pituitary growth hormone in thyroidectomized animals, these authors concluded that the action of thyroid deficiency upon brain is independent of its other effects.

Thyroid and Respiration.—The mechanism whereby thyroxin accelerates maturation is little understood. The more recent experimental evidence suggests that, unlike most other tissues, brain material removed from adult animals (mostly rats or guinea-pigs) treated with thyroxin or thyrostatic substances shows little or no change of in vitro respiration (Barker, 1951). However, in the young hyperthyroid rat, Fazekas and co-workers (1951) found that cerebral oxygen uptake measured in vitro began to rise sharply on the 7th day after birth instead of on the 10th, as in the control. By the 30th day it was some 8 days ahead, and the adult value was reached—but never thereafter exceeded—in 40 days instead of the normal 46. Thus the effect of thyroxin upon oxygen uptake in cerebral tissue is detectable only during periods of rapid differentiation.

Effects of Undernutrition and Thiouracil Derivatives.—The effects of thyroid deficiency are closely reproduced in experimental animals subjected to any acute dietary deficiency, except perhaps scurvy (McCarrison, 1921). Several groups of investigators, who have exposed rats or guinea-pigs to acute or chronic undernutrition sufficient to reduce body weight by 20% or 30%, have observed indications of hypothyroidism, including decreased weight and respiration of the gland, retention of colloid, involution of follicles, and sensitivity to administered thyrotropin (Rabinovitch, 1929; Stephens, 1940; Stephens and Belasco, 1940). Eayrs and Horn (1955) have observed that the growth of neuropil in rat brain is reduced in both inanition and thiouracil-induced hypothyroidism. Some of the consequences of undernutrition, such as anorexia, fall in metabolic rate, and depression of adrenal, reproductive, and thyroid activity, resemble those of hypophysectomy (Pomeranz and Mulinos, 1939; Mulinos and Pomeranz, 1940). On the basis of this evidence, it is therefore suggested that the retardation of the retinal lesion in the underfed mouse may well be the result of a reduction in thyroid activity. The re-

sults of propylthiouracil treatment upon body growth and retinal development are essentially similar to those of undernutrition. While the effects of the drug could be ascribed to direct interference with thyroxin secretion, and those of undernutrition to hypothyroidism consequent on pituitary depression, no definite distinction is possible on the present evidence.

Behavior of Brain and Retina. — Far fewer studies have been made of retina than of brain, but since both consist of highly specialized nervous tissue it is not surprising that functional parallels exist, as follows:

1. Retina has an even higher respiratory activity than cerebral cortex, and, like the latter, its principal source of metabolic energy is carbohydrate.

2. Administration of thyroxin to adult rats does not have the significant effect in vitro upon glucose utilization in the retina (Kornblueth, Yardeni-Yaron, and Wertheimer, 1953) or upon respiration in the brain (Fazekas and others, 1951) that it does upon tissues capable of a more flexible metabolic performance, such as voluntary muscle.

3. Thyroidectomy in newborn rats depresses the rate of growth of eyeball and brain much less than that of other organs of the body as a whole.

Further aspects of retinal behavior, described in the present work, also conform to the above parallel, in so far as comparative data are available, e. g.:

1. Thyroxin enhances the progress of the degeneration in the differentiating retina in a manner comparable with the effect of the thyroid hormone on the maturation of the central nervous system in amphibia (Kollros, 1943).

2. Pituitary growth hormone has no effect on either the degenerative process in mouse retina or on the somewhat retarded rate of development of brain and eye of the rat thyroidectomized at birth, though it accelerates somatic and cranial growth in both species. Thyroxin has a marked effect on both nervous tissues.

3. Though thyrostatic agents of the thiouracil type, administered before or after adult age is reached, have little or no effect upon cerebral respiration, either clinically (Sokoloff, Wechsler, Mangold, Balls, and Kety, 1953) or experimentally (Fazekas, 1946; Fazekas and others, 1951; Barker, 1951; Barker and Klitgaard, 1952), they undoubtedly delay maturation of both the eye and cerebral cortex of the rat (Fazekas and others, 1951; Eayrs and Taylor, 1951). A similar retardation of retinal maturation may account for the delayed onset of the lesion seen in some of the animals receiving propylthiouracil.

It is possible that the level of thyroid hormone may regulate the time of onset of a specific phase of differentiation with which retinal degeneration is associated; in the normal tissue additional thyroxin merely hastens maturation, but in the affected retina degeneration supervenes. The mechanism of the thyroxin effect is obscure; respiration is also augmented by dinitrophenol, but the mode of action is different and this substance does not affect the retina. In rats, thyroxin has been found to promote conversion of carotene to vitamin A and thence possibly to rhodopsin, but this synthesis, which begins at about 12 days after birth, may not be essential to tissue survival. However, a notable rise in cerebral metabolism is known to occur during the second 10 days after birth. Glycolysis gives way to respiration as the principal means of energy release from carbohydrate, while synthesis of phosphatides and proteolipide proteins increases sharply. The role of thyroxin in stimulating enzyme processes of this kind awaits further investigation.

Summary

Attempts were made to modify the course of a recessively inherited dystrophy of the visual cells of the mouse retina by administering large doses of various agents, including vitamins, hormones, amino acids, and intermediates of carbohydrate metabolism to the animals from shortly after birth.

Undernutrition and *n*-propylthiouracil were found to delay and thyroxin to advance the onset of the degenerative changes. The results are discussed in relation to what is known of the influence of these factors on the growth and maturation of nervous tissue.

None of the other agents affected the course of the dystrophy, but sodium L-glutamate destroyed the inner layers of the retina, which are not affected in the dystrophy.

Prof. P. C. Koller and Prof. H. McIlwain gave advice in the course of this work, and Mrs. D. B. Hatton and Miss D. Tremain gave technical assistance.

Royal College of Surgeons of England, Lincoln's Inn Fields.

BIBLIOGRAPHY

Asling, C. W.; Walker, D. G.; Simpson, M. E.; Li, C. H., and Evans, H. M.: Deaths in Rats Submitted to Hypophysectomy at an Extremely Early Age and the Survival Effected by Growth Hormone, Anat. Rec. 114:49-62, 1952.

Barker, S. B.: Mechanism of Action of the Thyroid Hormone, Physiol. Rev. 31:205-243, 1951.

——and Klitgaard, H. M.: Metabolism of Tissues Excised from Thyroxine-Injected Rats, Am. J. Physiol. 170:81-86, 1952.

Bruce, H. M., and Parkes, A. S.: Feeding and Breeding of Laboratory Animals: IX. A Complete Cubed Diet for Mice and Rats, J. Hyg. 47:202-208, 1949.

Brückner, R.: Spaltlampenmikroscopie und Ophthalmoskopie am Auge von Ratte und Maus, Docum. ophth. 5-6:452-554, 1951.

Buschke, W.: Dystrophic Cataracts and Their Relation to Other "Metabolic" Cataracts, Arch. Ophth. 30:751-762, 1943.

Dye, J. A., and Maughan, G. H.: Further Studies of the Thyroid Gland: V. The Thyroid Gland as a Growth-Promoting and Form-Determining Factor in the Development of the Animal Body, Am. J. Anat. 44:331-368, 1929.

Eayrs, J. T., and Horn, G.: The Development of the Cerebral Cortex in Hypothyroid and Starved Rats, Anat. Rec. 121:53-61, 1955.

——and Taylor, S. H.: The Effect of Thyroid Deficiency Induced by Methyl Thiouracil on the Maturation of the Central Nervous System, J. Anat. 85:350-358, 1951.

Evans, H. M.; Simpson, M. E., and Pencharz, R. I.: Relation Between the Growth Promoting Effects of the Pituitary and the Thyroid Hormone, Endocrinology 25:175-182, 1939.

Fazekas, J. F.: Cerebral Metabolism of Hyperthyroid, Thyroid-Deficient and Cretinous Rats, Fed. Proc. 5:26, 1946.

——Graves, F. B., and Alman, R. W.: The Influence of the Thyroid on Cerebral Metabolism, Endocrinology 48:169-174, 1951.

Hoskins, M.: The Effect of Acetyl Thyroxin on the Newborn White Rat, J. Exper. Zool. 48: 373-390, 1927.

Johnson, M. L.: The Effect of Vitamin A Deficiency upon the Retina of the Rat, J. Exper. Zool. 81:67-89, 1939.

Degeneration and Repair of the Rat Retina in Avitaminosis A, Arch. Ophth. 29:793-810, 1943.

Karli, P.: Rétines sans cellules visuelles: Recherches morphologiques, physiologiques et physiopathologiques chez les rongeurs, Arch. Anat. Strasbourg 35:1-75, 1952.

Keeler, C. E.: The Inheritance of a Retinal Abnormality in White Mice, Proc. Nat. Acad. Sc. 10:329-333, 1924.

On the Occurrence in the House Mouse of a Mendelizing Structural Defect of the Retina Producing Blindness, Proc. Nat. Acad. Sc. 12:255-258, 1926.

Kollros, J. J.: Experimental Studies on the Development of the Corneal Reflex in Amphibia: II. Localized Maturation of the Reflex Mechanism Effected by Thyroxin-Agar Implants into the Hindbrain, Physiol. Zool. 16:269-279, 1943.

Kornblueth, W.; Yardeni-Yaron, E., and Wertheimer, E.: Glucose Utilization of the Retina: II. Influence of Various Hormones on the Glucose Utilization of the Retina, A. M. A. Arch. Ophth. 50:500-505, 1953.

Kull, H.: The Late Embryonic Development of the Thyroid Gland of the Albino Rat, Anat. Rec. 32:133-138, 1926.

McCarrison, R.: Studies in Deficiency Disease, London, Hodder & Stoughton, Ltd., 1921, p. 150.

McEachern, D.: The Metabolism of Isolated Surviving Tissues from Animals Rendered Hyperthyroid with Thyroxine, Bull. Johns Hopkins Hosp. 56:145-179, 1935.

Mulinos, M. G., and Pomeranz, L.: Pseudo-Hypophysectomy: A Condition Resembling Hypophysectomy Produced by Malnutrition, J. Nutrition 19:493-504, 1940.

Newhouse, J. P., and Lucas, D. R.: To be published.

Noell, W. K.: The Effect of Iodoacetate on the Vertebrate Retina, J. Cell. & Comp. Physiol. 37:283-307, 1951.

Peterson, R. R., and Young, W. C.: The Problem of Placental Permeability for Thyrotrophin, Propyl Thiouracil and Thyroxine in the Guinea-Pig, Endocrinology 50:218-225, 1952.

Pomeranz, L., and Mulinos, M. G.: Pseudo-Hypophysectomy Produced by Inanition, Am. J. Physiol. 126:601, 1939.

Rabinovitch, J.: The Effect of Underfeeding on the Proliferative Activity of the Thyroid Gland in the Guinea-Pig, Am. P. Path. 5:87-90, 1929.

Ray, R. D.; Simpson, M. E.; Li, C. H.; Asling, C. W., and Evans, H. M.: Effects of the Pituitary Growth Hormone and of Thyroxin on Growth and Differentiation of the Skeleton of the Rat Thyroidectomized at Birth, Am. J. Anat. 86:479-516, 1950.

Salmon, T. N.: The Effect on the Growth Rate of Thyro-Parathyroidectomy in Newborn Rats and of the Subsequent Administration of Thyroid, Parathyroid and Anterior Hypophysis, Endocrinology 23:446-457, 1938.

———Effect of Pituitary Growth Substance on the Development of Rats Thyroidectomized at Birth, Endocrinology 29:291-296, 1941.

Scow, R. O., and Marx, W.: Response to Pituitary Growth Hormone of Rats Thyroidectomized on the Day of Birth, Anat. Rec. 91: 227-234, 1945.

———and Simpson, M. E.: Thyroidectomy in the Newborn Rat, Anat. Rec. 91:209-226, 1945.

———Simpson, M. E.; Asling, C. W.; Li, C. H., and Evans, H. M.: Response by the Rat Thyro-Parathyroidectomized at Birth to Growth Hormone and to Thyroxin Given Separately or in Combination, Anat. Rec. 104: 445-463, 1949.

Sokoloff, L.; Wechsler, R. L.; Mangold, R.; Balls, K., and Kety, S. B.: Cerebral Blood Flow and Oxygen Consumption in Hyperthyroidism Before and After Treatment, J. Clin. Invest. 32:202-208, 1953.

Sorsby, A.; Koller, P. C.; Attfield, M.; Davey, J. B., and Lucas, D. R.: Retinal Dystrophy in the Mouse: Histological and Genetic Aspects, J. Exper. Zool. 125:171-198, 1954.

Stephens, D. J.: The Effect of the Thyrotropic Principle of the Anterior Pituitary on the Thyroid of the Undernourished Guinea-Pig, Endocrinology 26:485-492, 1940.

———and Belasco, I. J.: Effect of Undernutrition on Thyroid Tissue Respiration of Guinea-Pig, Proc. Soc. Exper. Biol. & Med. 45:706-708, 1940.

Tansley, K.: Factors Affecting the Development and Regeneration of Visual Purple in the Mammalian Retina, Proc. Roy. Soc. Lond. 114:79-103, 1934.

The Effect of Vitamin A Deficiency on the Development of the Retina and on the First Appearance of Visual Purple, Biochem. J. 30:839-844, 1936.

An Inherited Retinal Degeneration in the Mouse, J. Hered. 45:123-127, 1954.

Todd, T. W.; Wharton, R. E., and Todd, A. W.: The Effect of Thyroid Deficiency upon Bodily Growth and Skeletal Maturation in Sheep, Am. J. Anat. 63:37-78, 1938.

Tusques, J.: Action de la thyroxine sur l'appareil visuel des têtards de rana esculenta, Compt. rend. Soc. biol. 143:332, 1951.

Wald, G.: The Biochemistry of Vision, Ann. Rev. Biochem. 22:497-526, 1953.

Walker, D. G.; Asling, C. W.; Simpson, M. E.; Li, C. H., and Evans, H. M.: Structural Alterations in Rats Hypophysectomized at 6 Days of Age and Their Correction with Growth Hormone, Anat. Rec. 114:19-36, 1952.

———Simpson, M. E.; Asling, C. W., and Evans, H. M.: Growth and Differentiation in the Rat Following Hypophysectomy at 6 Days of Age, Anat. Rec. 106:539-554, 1950.

Mikulicz's Disease of the Lacrimal Gland

D. F. MILAM Jr., M.D., Boston

Mikulicz's disease of the lacrimal gland is a rare disease of unknown etiology. Four specimens of this disease, found in the files of the Eye Pathology Department of the Massachusetts Eye and Ear Infirmary since 1896, are reported.

Johann Mikulicz [1] first described, in 1888, a chronic self-limited disease of unknown etiology involving the lacrimal and salivary glands. Clinically the patient presented painless swelling of the lacrimal, salivary, and palatine glands. No decrease in the function of these glands was noted: Indeed, copious salivation was described. Microscopic examination revealed the tissue of the submaxillary gland to consist primarily of small round cells. These cells lay close together or separated by a fine reticulum. Mitotic figures were seen in single large cells. Imbedded in the small round cells were apparently unchanged acini of the salivary gland. A similar picture was found on examining the lacrimal gland. This author rejected as further examples of the disease he described other cases with swelling of the lacrimal and salivary glands of demonstrable etiology.

There has been much confusion in terminology since the condition was first described, but, in general, the designation of Mikulicz's disease has been reserved for disease of unknown etiology of the lacrimal and salivary glands. Where the nature of the disease process could be determined, the designation has been Mikulicz's syndrome. Even where the use of Mikulicz's disease has been reserved for those cases of unknown etiology, it is probable from the microscopic description that more than one disease process has been included. Heath [2] described a case of Mikulicz's disease of unknown etiology, but his illustrations appear more likely to be of sarcoid than of the condition pictured by Mikulicz.

Morgan and Castleman, in 1953,[3] clearly described 18 cases of disease of the lacrimal and salivary glands which they believed to be the same disease originally described by Mikulicz. All of these were of unknown etiology and ran a clinically benign course. Each showed a typical histologic picture that permitted it to be readily separated from other lesions of the lacrimal and salivary glands. Some of these had previously been diagnosed as malignant tumors and treated accordingly.

Gross examination of the tissue from the lacrimal and salivary glands showed either diffuse or local involvement of the gland parenchyma. The regional lymph glands were not involved. The microscopic findings were diagnostic and similar regardless of which gland or glands were involved. None of the typical histologic features described were found in specimens of lacrimal and salivary glands with disease of known etiology. These characteristic microscopic changes were (1) typical islands of epithelial cells, representing the remnants of the duct epithelium, buried in sheets of small round cells; (2) deposition of a hyaline material in and between the cells of the epithelial islands (the amount of hyaline material increased with the known duration of the case); (3) preservation of the interlobular septa even in advanced cases.

Chronologically, the first evidence of the disease to be found in microscopic sections was the presence of lymphoid cells around the interlobular duct. Later the whole lobule

Received for publication June 11, 1956.

From the Eye Pathology Laboratory of the Massachusetts Eye and Ear Infirmary.

This study was supported by a grant from the National Institutes of Health, Division of Neurological Disease and Blindness.

was involved. The small round cells eventually displaced all of the glandular elements. Well-circumscribed lymph follicles were not present. Some lymphoid cells showed active mitoses. Eventually the only epithelial elements remaining were the epithelial and myoepithelial cells of the ducts. The epithelium lining the ducts in all cases showed characteristic changes. The nuclei became hyperchromatic; the cytoplasm, more basophilic. The number of nuclei within the duct epithelium increased, especially those of the myoepithelial cells. There was piling up and loss of polarity of cells. Eventually the duct was obliterated by epithelial and myoepithelial cells. Cell boundaries were indistinct, and the distinction between epithelial and myoepithelial cells was difficult. Infiltration of lymphoid cells between the epithelial cells was common. The remaining epithelial elements were called by the authors epimyoepithelial islands. Hyaline material was deposited in and about the epithelial cells of the islands of epithelial cells. Even in the advanced stage of the disease, the interlobular septa were preserved and were not invaded by the lymphoid cells.

Clinical Material

Material from four patients with enlargement of the lacrimal gland was available for study.

Case 1.—Male. Tumor of the lacrimal gland 18×29 mm. No further history obtainable.

Case 2.—White woman 39 years old. High myopia, old corneal scars. Vision with correction 20/50 O. U. For five or more years right upper lid had been prominent. There had been difficulty opening O. D. This condition had remained static. In September, 1937, examination showed large nontender soft tumor under right orbital ridge extending back into the orbit. At operation a tumor composed of firm sticky tissue like dark grayish tapioca was uncovered. No definite capsule was present. Biopsy diagnosis was inflamed mixed tumor of the lacrimal gland. Exenteration of orbit was refused. Local removal of tumor was accomplished. One month later a tumor was palpable in the region of the left lacrimal gland. This gradually increased in size. One year later this was removed. At operation a well-encapsulated grayish mass in the region of the lacrimal gland was encountered and removed. The pathologic diagnosis at this time was papillary crystadenoma lymphomatosis. There has been no recurrence of the disease. Both eyes have been dry since the operation.

Case 3.—Fourteen-year-old boy. For one and one-half years a mass had been present in the right upper eyelid. Vision was 20/20 O. U. Ocular examination was entirely normal. Six years previously he had developed right submaxillary gland hypertrophy that resulted in a ranula three years later. At operation, a mass above the lateral canthus, in the region of the gland, was removed. Gross examination of the cut surface revealed glistening tan lobulated surfaces. Histologic diagnosis was Mikulicz's disease of the lacrimal gland.

Case 4.—Negro woman, 55 years old. For one year O. D. had been more prominent than O. S. Exhaustive x-ray and laboratory studies were negative. Vision O. D. was 20/30, and vision O. S. was 20/20. The exophthalmometer readings were 23 O. D., 17 O. S. There was limitation of ocular movement O. D. in all fields. There was a palpable tumor in the region of the right lacrimal gland. The eye was not dry. At operation a soft encapsulated lobulated tumor was found. Biopsy specimen showed typical findings of Mikulicz's disease. One month after operation the proptosis had largely disappeared.

Pathology

The microscopic picture in the four cases presented above was similar in all respects to the cases of Mikulicz's disease described by Morgan and Castleman.[3] Dr. Morgan[3,4] reviewed the microscopic slides in the present cases and concurred in the diagnosis.

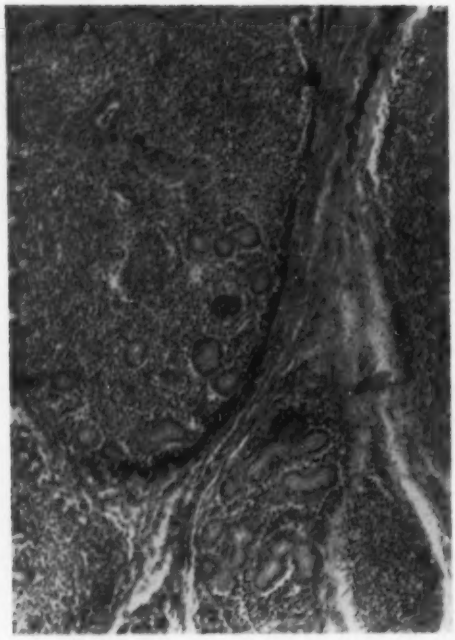


Fig. 1 (Case 3).—Sheets of small round cells, remaining acini, interlobular septa spared. Hematoxylin and eosin; 16 mm. objective.

Case 2 was included in the studies by Morgan and Castleman.

In all four cases the glandular elements were largely replaced by sheets of small lymphocytes with scanty cytoplasm and a large nucleus with bunched chromatin. Occasionally an immature lymphocyte was seen. A rare mitosis was seen. No germinal centers were found. The lobular arrangement of the gland was maintained. The septa were not invaded by the lymphoid cells. Lobules showing early involvement were found in close proximity to those almost destroyed by the disease. Where the involvement was more marked, only the ducts were left. The epithelial and myoepithelial cells of the ducts showed an increase in the number of nuclei, loss of polarity, indistinct cell boundaries, and infiltration with lymphocytes. The basement membrane around the ducts was still prominent at this stage. In a more advanced stage the epithelial remnants persisted as islands of epithelial and myoepithelial cells in a sheet of small round cells. At an early stage hyaline material was seen in and around the cells of the epithelial islands. This became prominent in some epithelial islands. In Cases 2 and 3 there was hyalinization of the stroma.

Comment

The histologic picture of Mikulicz's disease as described by Morgan and Castleman [3] is characteristic, and, once recognized, it should be readily differentiated from

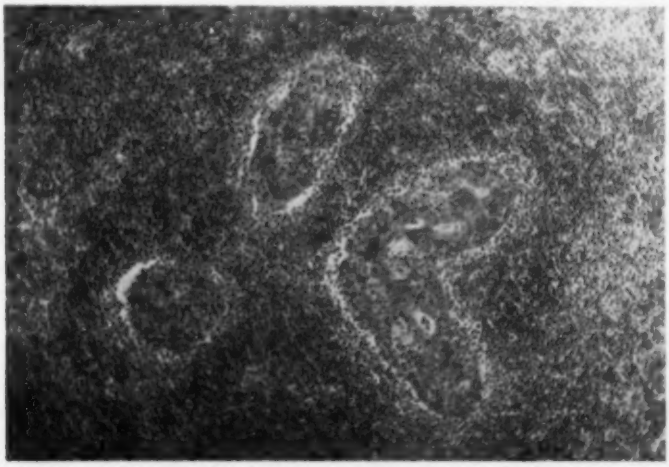


Fig. 2 (Case 3).—Epimyoepithelial islands. Hematoxylin and eosin; 16 mm. objective.

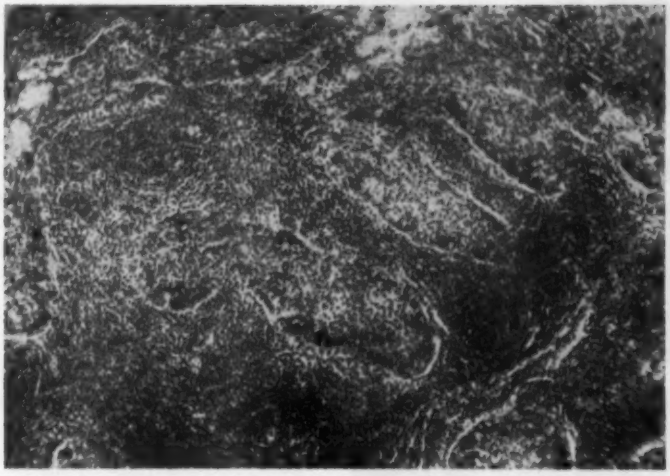


Fig. 3 (Case 2).—Epimyoepithelial islands. Hematoxylin and eosin; 16 mm. objective.

chronic inflammation, adenocystoma lymphomatosum, leukemia, lymphoma, and mixed tumors of the seromucinous glands. No etiology is known for this disease. Some authors [3,4] feel that disease of the epithelial structures is primary, the lymphocytic infiltration secondary.

In the original case described by Mikulicz, the lacrimal, salivary, and palatine glands were involved. Mueller [5] recently diagnosed this condition in a mass on the epiglottis. He believed that this arose from the seromucinous glands in this location. Small seromucinous glands are widely distributed under the epithelium of the conjunctiva, sinuses, nasopharynx, and mouth in addition to the large glands, lacrimal and salivary, of this same type.

Accessory lacrimal gland tissue may be widely distributed in the lids and orbit. Accordingly, this disease must be suspected with any lid and orbital tumor.

None of the present group of patients had a dry eye. In Mueller's [5] case of Mikulicz's disease of the epiglottis the lacrimal glands were enlarged to palpation

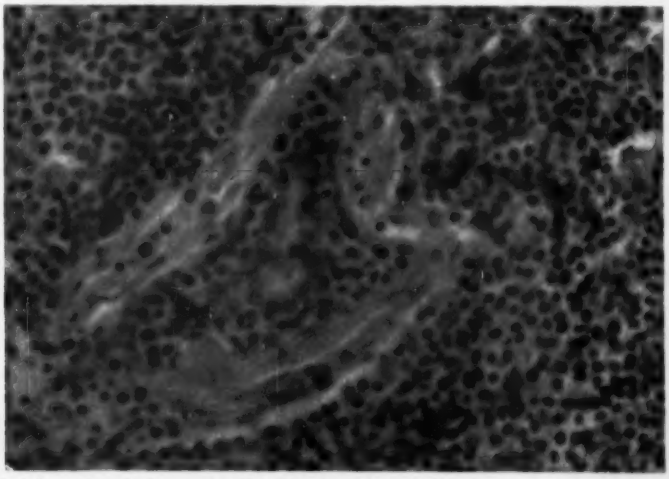


Fig. 4 (Case 3).—Epimyoepithelial island with hyalin. Hematoxylin and eosin; 40 mm. objective.

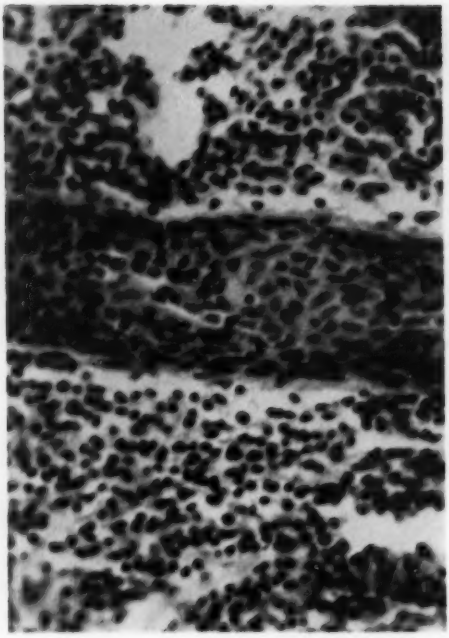


Fig. 5 (Case 4).—Intralobular duct occluded by proliferation of epithelial cells. Hematoxylin and eosin; 40 mm. objective.

and the patient complained of burning of his eyes but no corneal changes suggestive of a dry eye were present. The lacrimal secretion was not measured. Morgan [3] feels that there is a close relationship between Mikulicz's disease and Sjögren's syndrome. While this has not been proved, it would seem logical to expect a marked diminution of tears after much of the gland tissue is destroyed.

Summary and Conclusions

Four cases of Mikulicz's disease of the lacrimal and salivary glands are presented.

This disease is diagnosed by histologically finding the typical epimyoepithelial islands, intraductal proliferation of epithelial and myoepithelial cells, and sheets of lymphoid cells.

The condition is benign, self-limited, and of unknown etiology.

This disease may be found in any of the seromucinous glands.

The diagnosis of Mikulicz's disease should be considered in any tumor of the lacrimal gland and orbit.

Dr. L. R. Dame (Case 3) and Dr. Virgil Casten (Case 4) granted permission to report their private cases.

243 Charles St. (14).

REFERENCES

1. von Mikulicz, J.: Concerning a Peculiar Symmetrical Disease of the Lacrimal and Salivary Glands, M. Classics 2:165-186 (Oct.) 1937.

2. Heath, P.: Mikulicz's Disease and Syndrome, Am. J. Ophth. 31:955-964 (Aug.) 1948.

3. Morgan, W. S., and Castleman, B.: A Clinicopathologic Study of Mikulicz's Disease, Am. J. Path. 29:471-503 (May-June) 1953.

4. Morgan, W. S.: The Probable Systemic Nature of Mikulicz's Disease and Its Relation to Sjögren's Syndrome, New England J. Med. 251: 5-10 (July 1) 1954.

5. Mueller, W.: Personal communication to the author.

The Use of the Antibacterial Drugs and Streptokinase

Administered Intramuscularly in Enucleation of the Eye.

JOSEPH M. MILLER, M.D.; DAVID W. PARKE, M.D.; JOHN A. SURMONTE, M.D.;

MILTON GINSBERG, M.D., Fort Howard, Md., and FRANK B. ABLONDI, A.B., Pearl River, N. Y.

The study of the microenvironment in inflammation and edema is a new field. Traditionally this region has been regarded correctly as a defense curtain, since it inhibits the spread of infection. The preservation of this membrane has been considered a basic surgical necessity.

The advent of the antibacterial drugs has produced a change in thought about this defense barrier. These substances are of little value in the treatment of abscesses, walled-off cellulitis, and similar inflammatory processes. Being carried by the blood, the antibacterial drugs cannot pass through the membrane from without anymore than can pathogenic bacteria from within.

The edema fluid present in inflammation and in edema alone contains large quantities of fibrin. Coagulation of this substance in the tissue fluids and the formation of thrombi in the arteries, capillaries, veins, and lymphatics help to localize the damaged area. This localizing process, in which precipitation of fibrin occurs, produces what many surgeons term a limiting membrane.

Streptokinase indirectly causes the lysis of fibrin through the activation of the plasminogen-plasmin mechanism in the euglobulin fraction of the blood serum. Since edema fluid and the limiting membrane of a localized inflammation contain large amounts of fibrin, streptokinase was administered intramuscularly in an effort to change the chemical nature of the edema fluid and the limiting membrane.[1] The streptokinase had an apparent lysing effect on the membrane, for antibacterial drugs given concomitantly resolved the associated infection.

After enucleation of the eye, the orbit and adjacent conjunctival tissues often become very edematous, particularly in patients in whom there has been much preoperative inflammation. The use of streptokinase intramuscularly seemed natural to ameliorate or prevent this complication. An antibacterial drug must be given concurrently, since the composition of the defense barrier apparently is changed by the administration of streptokinase intramuscularly.

Streptokinase-streptodornase (Varidase) was used as the source of streptokinase, since a pure preparation of streptokinase has not yet been made. Although this preparation contains streptokinase and streptodornase, the streptodornase can be disregarded for therapeutic purposes. Streptokinase-streptodornase was dissolved in isotonic saline so that the final concentration was 10,000 units of streptokinase per cubic centimeter. The solution must be stored in a refrigerator when not being used. A fresh solution was made daily. Five thousand units in 0.5 cc. of isotonic saline was injected twice daily for a total of six doses or longer if necessary.

Received for publication July 17, 1956.

From the Surgical Service, Veterans Administration Hospital (Drs. Miller, Parke, Surmonte, and Ginsberg), and the Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y. (Mr. Ablondi).

Report of Cases

CASE 1.—A 35-year-old white man was admitted to the hospital on Sept. 27, 1954, for enucleation of the left eye. He had sustained multiple injuries of the body, many wounds of both eyes from sand and cinders, and a burn of the left eye when a tank containing ammonia exploded. A lamellar keratoplasty was done on the left eye in 1952, but the cornea subsequently became opaque. Severe photophobia in the right eye and bilateral epiphora had been present since 1952.

Vision in the right eye was 20/30, and in the left eye sight was limited to light perception with good projection. The lids, conjunctivae, and corneas of the eyes were studded with imbedded small foreign bodies. A vascularized corneal leukoma was present in the left eye.

Enucleation of the left eye was done on Sept. 28, because it was thought that much of the patient's difficulty with the right eye might have been due to a reflex sympathetic irritation originating in the left eye. The lids were sutured after enucleation because the conjunctiva was severely edematous, the result of the removal of multiple foreign bodies from it. Sulfisoxazole (Gantrisin), 1.0 gm., was given by mouth four times a day from Sept. 28 through Nov. 11. The lid sutures were removed on Oct. 4, because of severe pain and prolapse of the conjunctiva between the sutures. Five thousand units of streptokinase in 0.5 cc. of isotonic saline was given intramuscularly twice a day from Oct. 4 to Oct. 7, for a total of six doses. The edema of the lids decreased remarkably, but the prolapse of the edematous conjunctiva became relatively more pronounced. On Oct. 7 a Snellen suture was placed in the lids. On Oct. 11 the sutures came out spontaneously. Sutures were placed again on Oct. 12. The sutures were removed on Oct. 19. The edema subsided gradually and disappeared on Oct. 19. The epiphora and photophobia of the right eye stopped. A custom-fitted conformer was inserted into the socket on Oct. 21. The patient was discharged from the hospital on Nov. 5.

CASE 2.—A 64-year-old white man was admitted to the hospital on Nov. 4, 1954, with a blind painful left eye, the result of glaucoma secondary to an occlusion of the central retinal vein. Five thousand units of streptokinase in isotonic saline was given intramuscularly twice a day from Nov. 6 through Nov. 10, for a total of 10 doses. On Nov. 8 enucleation of the left eye was done and a No. 18 plastic sphere was implanted. At the time of the first change of dressing, on Nov. 9, inflammation and edema were minimal in degree. The continuous conjunctival suture of 00000 black nonabsorbable surgical (silk) suture was readily visible. The suture was removed on Nov. 16. A custom-fitted heavy plastic conformer was inserted into the socket on Nov. 17. The patient was discharged from the hospital on Nov. 22.

CASE 3.—A 27-year-old white man was admitted to the hospital on Jan. 3, 1955, with the fifth recurrence of a generalized nongranulomatous uveitis of the left eye. In 1952 he had had a diathermy barrage for an inflammatory retinal detachment elsewhere. Later, he had a scleral resection and the globe was penetrated, resulting in a loss of the vitreous humor. The eye was painful, photophobic, and red. Vision was reduced to bare light perception. There was much ciliary injection, many fine keratitic precipitates, and a 2+ aqueous ray. Rubeosis of the iris was marked, and a swollen hypermature complicated cataract was present. The right eye was normal.

Sulfisoxazole, 1.0 gm., was given by mouth four times a day from Jan. 3 through Jan. 12. Five thousand units of streptokinase in 0.5 cc. of isotonic saline was given intramuscularly twice a day from Jan. 4 through Jan. 7, for a total of eight doses. On Jan 6 enucleation of the left eye was done and a No. 18 plastic sphere implant was inserted into the socket. The conjunctival suture was visible from the time

of the first change of dressing, on Jan. 8. On Jan. 10 a mild edema was noted. The suture was removed on Jan. 11. A custom-fitted conformer was inserted on Jan. 13. The patient was discharged from the hospital on Jan. 14.

CASE 4.—A 29-year-old white man was admitted to the hospital on Feb. 20, 1955, for an enucleation of the left eye. He had had recurrent attacks of iridocyclitis since 1942. In 1953 he sustained a corneal laceration followed by a traumatic cataract. The eye became phthisical and, just before admission, red and painful. Light perception was absent. The right eye was normal. Five thousand units of streptokinase in 0.5 cc. of isotonic saline was given intramuscularly twice a day from Feb. 20 through Feb. 23, for a total of seven doses. Enucleation of the left eye and the insertion of a No. 18 plastic sphere implant into the socket were done on Feb. 21. Sulfisoxazole, 1.0 gm., was given by mouth four times a day from Feb. 21 through Feb. 24. Inflammation and edema were minimal in degree on Feb. 23. The suture was removed on Feb. 25, and a custom-fitted heavy plastic conformer was inserted. The patient was discharged from the hospital on Feb. 25, 1955.

CASE 5.—A 37-year-old white man was admitted to the hospital on Feb. 21, 1955, for enucleation of a phthisical right eye. He had incurred a wound of the right eye in 1936. Since that time, the eye had been blind. After the third spontaneous hyphemia, enucleation was recommended. Five thousand units of streptokinase in 0.5 cc. of isotonic saline was given intramuscularly twice a day from Feb. 21 through Feb. 26, for a total of 11 doses. Enucleation of the right eye was done, and a No. 18 plastic sphere implant was inserted into the socket on Feb. 23. Sulfisoxazole, 1.0 gm., was given by mouth four times a day from Feb. 23 through March 1. A moderate degree of inflammation and edema of the conjunctiva was noted postoperatively. On March 2 the sutures were removed and a custom-fitted conformer was inserted. The patient was discharged from the hospital on March 2.

Comment

Enucleation of the eye is most commonly followed by at least a moderate degree of reaction in the conjunctiva with edema. Not infrequently, prolapse of the conjunctiva occurs. Although this complication rarely impairs the result, the convalescence is prolonged and fitting of the permanent prosthesis is delayed. In 16 patients who had enucleation with insertion of plastic sphere implants and who had not been treated with streptokinase, all had edema of the conjunctiva ranging from moderate to severe. Five patients had a prolapse of the conjunctiva, and, of these, two required secondary lid closure with Snellen sutures. In all patients, fitting of a custom-made conformer was delayed until at least the 14th postoperative day.

The first patient in the group given streptokinase was treated with the drug after the enucleation was done, and the conformer was fitted on the 23d postoperative day. The next four patients were given streptokinase before the enucleation was done, and the conformer was fitted on the fifth, seventh, fourth, and seventh postoperative days. A considerable improvement in results was noted when the patients were treated with streptokinase before the enucleation was done.

The reactions to the intramuscular administration of streptokinase were minimal.[1] In a recent group of 64 patients given streptokinase in this manner in the treatment of infection and edema, excellent results were obtained in 45, good results in 17, and poor results in 4. The four poor results were obtained in one patient with extensive decubitus ulcers which were resistant to all forms of treatment, in two patients with arteriosclerotic vascular disease with gangrene in whom the blood supply was poor, and in one patient with thrombotic hemorrhoids who was given insuffi-

cient treatment. An aggravation of the infection was not seen in any of the patients. In patients with granulating wounds, healing was hastened by the reduction of surrounding induration. A delay in healing was not seen in any of the patients. A rise in temperature attributable to the administration of streptokinase was noted in about 10% of the patients. Pain and tenderness at the site of injection were found in about 60% of the patients but disappeared in 24 to 48 hours after the injections were stopped. The formation of a granuloma was not seen in any of the patients. A significant change in the white blood cell count or the differential count was not observed. A significant prolongation of the prothrombin time was not found. Fibrinolysis as determined by the whole blood technique was not observed, in periods of 72 hours after the fifth injection of streptokinase, on the third day of treatment. Hemorrhage and the formation of hematomas or petechiae were not seen. Streptokinase should not be given intramuscularly to patients with defects in the clotting mechanism, owing to the possibility of hemorrhage. The administration of antihistaminic drugs was not necessary. The routine for patients undergoing enucleation must include the administration of antibacterial drug and streptokinase intramuscularly starting about 48 hours before operation. The choice of the antibacterial agent will depend upon the bacteria present and/or the preference of the surgeon. Five thousand units of streptokinase in 0.5 cc. of physiologic saline should be given intramuscularly twice a day for three days—longer if it is necessary. The treatment of patients with streptokinase intramuscularly before and after operation has given the best results.

The intramuscular injection of streptokinase, by producing a socket with little inflammation and edema, has shortened the period of convalescence and has hastened the fitting of a conformer and a permanent prosthesis. The fitting of a permanent prosthesis at as early a date as possible is important, since it helps to reduce the number of mild contractural deformities of the superior fornix and the inferior fornix of the conjunctiva and to prevent untoward psychological changes.

Summary

The administration of an antibacterial agent and streptokinase intramuscularly has improved the results in patients who have had an enucleation of the eye. Further investigation of the use of these agents in patients having an enucleation of the eye is recommended.

Veterans Administration Hospital.

REFERENCE

1. Miller, J. M.; Surmonte, J. A.; Ginsberg, M., and Ablondi, F. B.: Clinical Experience with the Injection of Streptokinase in the Treatment of Infection and Edema, Maryland M. J. 4:188-193 (April) 1955.

Localization of Intraocular Foreign Bodies by Roentgen Examination

Practical Procedure

FERNANDO E. ROSAS, M.D., Yucatan, Mexico

Technique

1. Take plain films: front and side views of the suspected eye.

2. Reference lines: With some drops of 0.5% tetracaine (Pontocaine) solution anesthetize the eye, in order to attach at the sclerocorneal limbus the regular nonabsorbable surgical (silk) Atraumatic suture needles (3/8 circle 5/8 in. long, preferably).* The needles are passed through the conjunctiva and Tenon's capsule as close as possible to the cornea, starting about 1.5 mm. above and below the 3 o'clock or 9 o'clock position on the cornea, trying to mark the limbus surrounding the cornea in order to get its center.

3. Immediately take the following films:

A. Front view: looking straight ahead, both orbits; central ray focused on the center of the cornea
B. Front view: looking right, both orbits
C. Front view: looking left, both orbits
D. Front view: looking up, both orbits
E. Front view: looking down, both orbits

The films B, C, D, and E should be taken without changing the position of the patients' head, just changing the gaze.

F. Side view: looking straight ahead; central ray focused on the limbus of the cornea perpendicular to the axis of the eye.

If the films have been taken at the suggested positions, the reference needles will show in the frontal views a circle and in the side view a straight line. The Crookes tube is placed 60 cm. from the eye. The distance from the eye to the film should be 6 cm.; therefore a reduction by 1/10 is required in measurements going away from the central ray; 1/10 is added in the opposite direction.

4. Draw the diagrams on the films: Draw a line uniting both frontomalar sutures. Construct the perpendicular to this line from the foreign body, on the front views B, C, D, and E. If the foreign body is intraocular, in or attached to the structural layers of the eye, it will be noted that (1) in the front views B and C, the perpendicular changes its place, being nearer or farther from the frontomalar suture of the examined eye; (2) in the front views D and E, the length of the perpendicular line varies, being shorter or longer.

All of these displacements of the foreign body can be measured in millimeters. It is not possible to observe these changes only when the foreign body is in the center of rotation of the eye.

5. On the front view A and side view F films, the eye is drawn, taking as reference lines the needles used and the average dimensions of the normal eye, which according Wolff are the following: front view A, radius of the cornea 6 mm.; front view A, radius of the equatorial plane 11.5 mm.; side view F, radius of the vertical meridional plane 11.75 mm.

To find the center of the latter, cross the line after resting the compass at the 12 and 6 o'clock positions of the corneal limbus, marked by the upper and lower portion of the needles, and with an aperture of 11.75 mm.

Received for publication May 31, 1956.

*Vergara suggested the use of the regular Atraumatic silk suture needles as reference lines surrounding the cornea. Further application of this suggestion was developed for this procedure.

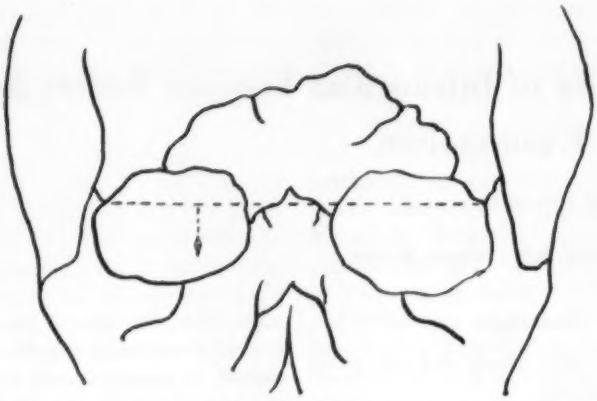


Fig. 1.—Diagram drawn on x-ray film. Right eye; front views B, C, D, and E. Frontomalar suture line and its perpendicular determined by the position of the foreign body.

The radius of the horizontal section representing the horizontal meridional plane is also 11.75 mm.

6. On the front view A, we can consider the cornea as a clock with every hour space divided into four quarters of an hour, 15, 30, 45, considering only the hour hand. The situation of any meridional plane can be read in hours and fractions of an hour, referring to that nearest to the foreign body.

7. On the front view A, trace the projection of the meridional plane of the eye which passes through the geometric centers of the eye and the foreign body. Measure in millimeters the shortest distance between the center of the foreign body and the equator of the eye, and reduce $\frac{1}{10}$.

8. On the side view F, trace a line passing through the centers of the eye and the foreign body, projecting the latter on the nearest portion of the vertical meridian of the eye; it also provides the directional approach into the eye to locate the foreign body. With a regular protractor, take the distance in degrees from the sclerocorneal limbus to the center of the foreign body projected on the surface of the eye; dividing by 5 and reducing $\frac{1}{10}$ provides the length of the meridian in millimeters. This is the same distance as that corresponding to the meridian where the foreign body is located.

9. On the side view F, measure the shortest distance in millimeters between the center of the foreign body and its projection on the surface of the globe. If this projection falls into the limbus or 3 mm. outside of it, it becomes necessary to reduce $\frac{1}{10}$ the distance under consideration. If it falls 20 mm. or more outside of it, it becomes necessary to add $\frac{1}{10}$ of same. Between 3 and 20 mm. no correction is necessary. Compare this distance with that obtained in front view A (Number 7). Select the smaller of the two, which will be close to the true value, having a possible error of 1 mm. at its maximum.

10. If the foreign body is situated in the horizontal meridional plane of the eye, it becomes necessary to draw this section separately (mentioned as horizontal section in Example 3 [Fig. 4]). Trace the diameter of the cornea, and, resting the compass on the two ends of this diameter, representing 3 and 9 o'clock on the corneal clock, with an aperture equal to its radius, 11.75 mm., cross the lines to obtain the center of the horizontal meridional section.

Transpose to the drawn horizontal section the projection distances from the center of the foreign body to the vertical meridional and equatorial planes of the eye, obtained from views A and F.

On the front view A reduce $\frac{1}{10}$. On the side view F add $\frac{1}{10}$ if the foreign body is in front of the equatorial plane and reduce

1/10 if it is behind it. In the equator no correction is necessary.

Cross the perpendicular lines as shown in the diagram of the horizontal section to locate the foreign body. Trace the line passing through the centers of the horizontal section and the foreign body, projecting the latter on the nearest portion of the horizontal meridian of the eye.

Take the distance in degrees from the sclerocorneal limbus to the center of the foreign body projected on the surface of the eye; dividing by 5 provides the length in millimeters of the horizontal meridian where the foreign body has been projected.

Take the shortest distance in millimeters between the center of the foreign body and its projection on the horizontal meridian of the eye, in order to obtain its localization as it is shown in Example III.

11. When the foreign body is situated in the horizontal or vertical meridional planes, the measurements obtained are exact. In any other meridional plane there is a small error of about 1 mm., which is maximum midway between the horizontal and the vertical meridional planes of the eye. If the foreign body is closer to the vertical meridional plane, the drawings on the films are accurate enough. If it is nearer to the horizontal meridional plane, a separate drawing of the horizontal section will give more accurate results.

The small error is usually compensated, considering that we have taken as reference the center of the foreign body. According to Shipman and associates,[1] 85.7% of foreign bodies are magnetic, and MacMillan [2] states that 15% are in the vitreous while the rest are near the surface of the globe. By the sound and sensation of the metal touching the magnet or the forceps, this little error may be corrected, giving a sufficiently accurate measurement to localize any radiopaque intraocular foreign body in relation to the meridional plane, and also it is possible to obtain the distance in millimeters between the foreign body and the vertical (nasal or temporal) and horizontal (above or below) meridional planes and the equatorial (in front or behind) plane of the eye.

12. Size of the foreign body: On the front view A and side view F films, measure the two largest dimensions in millimeters of the foreign body and arrange these four measurements in a series from the largest to the smallest. For practical purposes, we then consider the first as the length, the second the width, and the fourth as the thickness of the foreign body. The third may be ignored.

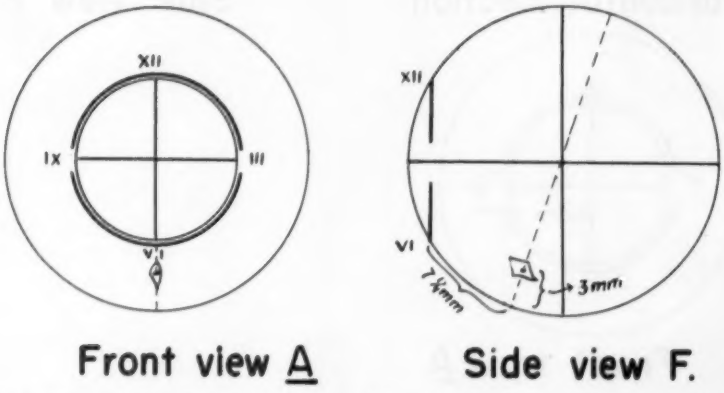


Fig. 2 (Example 1).—Report: Radiopaque intraocular foreign body situated in the meridional plane crossing through 6 hours of the corneal clock, to 7.25 mm. from the sclerocorneal limbus and 3 mm. from the scleral wall. Size of the body: 2.75 by 1.25 by 1 mm. Scale of this drawing is 2:1. Diagnosis: Intraocular foreign body situated in the vertical meridional plane.

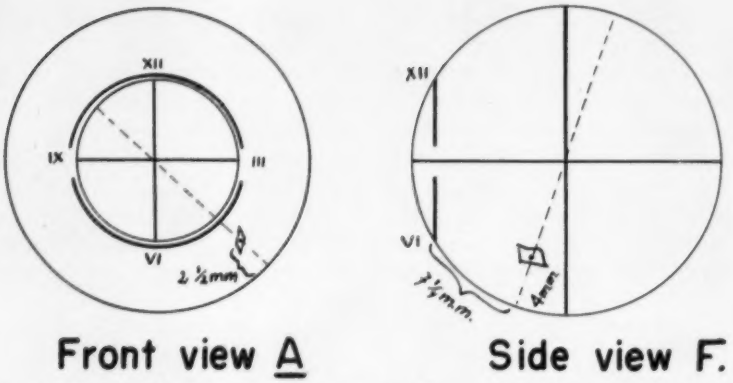


Fig. 3 (Example 2).—Report: Radiopaque foreign body situated in the meridional plane, crossing through 4:30 hours of the corneal clock, to 7.25 mm. from the sclerocorneal limbus and 2.5 mm. from the scleral wall. Size of the body: 2.25 by 1.25 by 0.5 mm. Scale of this drawing is 2:1. Diagnosis: Intraocular foreign body situated in an oblique meridional plane.

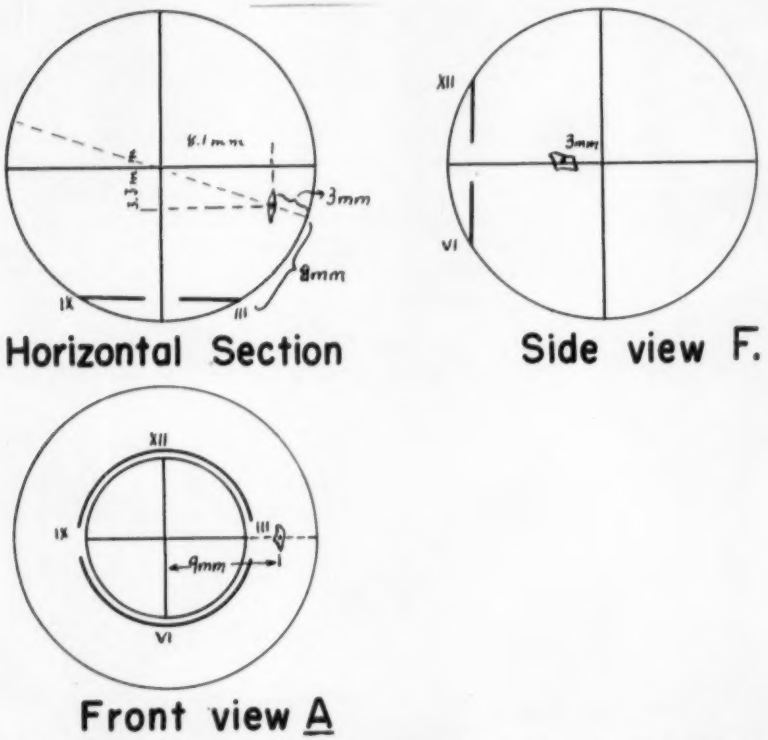


Fig. 4 (Example 3).—Report: Radiopaque intraocular foreign body situated in the meridional plane crossing through 3 hours of the corneal clock, to 8 mm. from the sclerocorneal limbus and 3 mm. from the scleral wall. Size of the body: 5 by 2 by 1 mm. Scale of this drawing is 2:1. Diagnosis: Intraocular foreign body situated in the horizontal meridional plane.

Examples

The technique has been applied in three cases so far (those in which existed a possibility of saving the eye), and it has proved successful in each one.

All the drawings were magnified in order to make the illustrations as clear as possible. In routine practice it is wise to draw the average dimensions of the normal eye.

In cases of magnetic foreign bodies, which are the most frequently encountered and are easier to extract, the correction of $\frac{1}{10}$ in the measurements given above could be dispensed with for practical purposes.

Summary and Conclusions

A simple technique is described for localization of radiopaque intraocular foreign bodies.

Nontraumatizing and practical, the technique only requires the usual x-ray machine and regular silk Atraumatic suture needles.

Applied in only three cases so far (those in which existed a possibility of saving the eye), it has proved successful in each one.

This technique may be helpful in places where special equipment is not available, since extraction of intraocular bodies is generally considered an emergency operation.

Calle 69, No. 570 A, Merida.

REFERENCES

1. Shipman, J. S.; Delaney, J. H., and Seely, R. H.: Magnet Extraction of Foreign Bodies, Am. J. Ophth. 36:620-628 (May) 1953.

2. MacMillan: Unpublished data, February, 1956.

3. Vergara, L.; Ramirez, A., and Arenas, F.: Heridas penetrantes del globo ocular: Cuerpos extraños intraoculares; Oftalmia simpática, An. Soc. mex. oftal. 22:23-31 (Jan.-March) 1948.

4. Wolff, E.: The Anatomy of the Eye and Orbit, Ed. 4, New York, The Blakiston Company, 1954, p. 30.

The Role of Intraocular Pressure in the Development of the Chick Eye

II. Control of Corneal Size

ALFRED JOSEPH COULOMBRE, Ph.D., New Haven, Conn.

Introduction

The increase in size of the vertebrate eye as a whole is regulated by a number of factors. Thus, the results of heteroplastic transplantations of amphibian eye primordia by Harrison[1] and Twitty and Schwind[2] have implicated genetic factors. In addition to genetic factors, nutritional factors may influence the enlargement of the amphibian globe.[3,4] Recent work with the chick embryo has revealed two additional factors. Not only is intraocular (vitreal) pressure a cardinal factor influencing the increase in the size of the eye, as shown by Weiss and Amprino[5] and me,[6,7] but the resistance to expansion offered by the eye wall as it elaborates cartilage and collagen appears to be important in progressively decreasing the rate of ocular expansion as development proceeds.[7]

If we turn our attention from the eye as a whole to its parts, we find much observational and experimental work supporting the idea that harmonious size and shape relationships are maintained among the different eye components throughout the period of eye development (summarized by Twitty).[3,8] The factors underlying this mutual adaptation of parts are probably diverse. From among the known or possible factors intraocular pressure has been singled out for study in the present series of investigations. Since this factor is important for the increase in the size of the eye as a whole, it is of interest to know to what extent it influences the increase in size and the change in shape of each component of the developing eye. The present paper reports data on the role of vitreal pressure in relation to the change in size and shape of the cornea.

Experimental Method

Chick embryos from eggs incubated at 37.5 C in a forced draft incubator were used in this investigation. All ages are given as days of incubation.

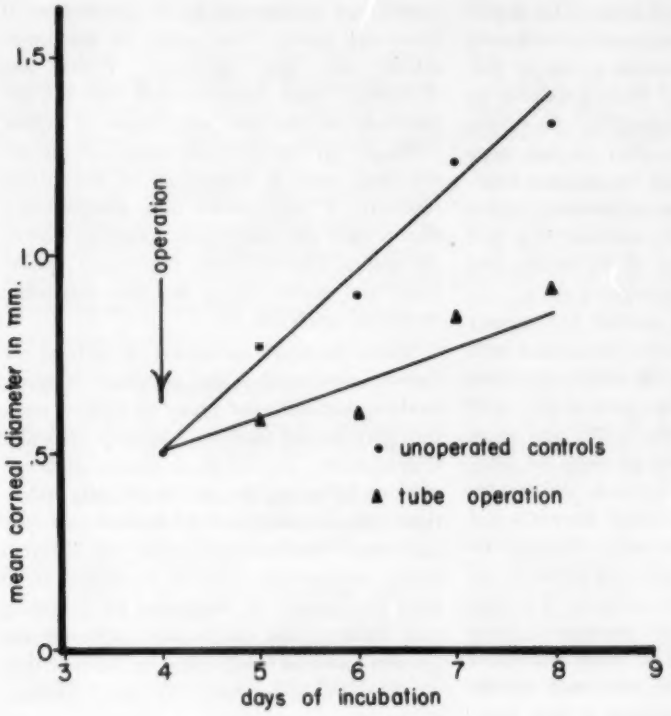
The operations described below were performed at the end of the fourth day, and periodic observations were made until the eighth. This period of development should provide maximal size differences, since the chick eye increases most rapidly in size between the fourth and eighth days.[6] Because the embryo lies on its left side on top of the yolk at the end of the fourth day, all operations were performed on the right eye.

The four series of eyes described below were examined in the same manner. A group of embryos was killed on each of the four days following the operation. The nasotemporal diameter of the cornea was measured in the freshly enucleated eye, and this was used as an index of corneal size. All measurements were made with a calibrated filar ocular micrometer and expressed to the nearest 0.1 mm. Some specimens from each group of eyes were fixed in

Received for publication Sept. 24, 1956.

Department of Anatomy, Yale University School of Medicine.

This investigation was supported in part by a research grant (B-870) from the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, Public Health Service, and in part by a grant from the James Judson Brown Memorial Fund of Yale University School of Medicine.



The corneal diameters of unoperated on and of intubated eyes are plotted against incubation age. Each point represents the mean value for a minimum of 10 cases.

Rossman's fluid, sectioned at 5.0μ, and stained with hematoxylin and eosin.

Eyes Not Operated On.—A reference series was provided by the left eyes of all the embryos used, since these developed without operative interference. The mean corneal diameter almost tripled during the four-day interval under consideration (Fig.).

Intubated Eyes.—To assay the role of intraocular pressure in the observed expansion of the cornea, vitreal pressure was reduced, during the period under investigation, by introducing a minute glass capillary tube (length, 3.0 mm.; outside diameter, 0.4 mm.; inside diameter, 0.25 mm.) through an incision in the wall of the four-day eye in such a way that one end rested in the vitreous body and one end in the amnionic cavity. The tube, which was left in place, allowed egress of vitreous humor and prevented the development of the tangential forces that normally act on the developing eye wall in the presence of an expanding vitreous body.

The intubation operation was performed on the right eyes of 43 chick embryos at four days of incubation. At daily intervals for the ensuing four days a group of 10 or 11 of these embryos was killed and the eyes were examined as described above. The mean values for corneal diameter on each postoperative day were significantly below the mean values for unoperated on contralateral eyes at the corresponding age (the *t*-test yielded values of $P=0.001$). In contrast to the tripling of corneal diameter over the four-day period which was observed in the unoperated on eyes, the intubated group showed somewhat less than a twofold increase. Histologic sections reveal that the corneas of intubated eyes become thicker than those of unoperated on eyes of comparable age. This relative increase in thickness is accounted for principally by the added thickness of the stroma and of Bowman's membrane.

Temporarily Intubated Eyes.—To determine the effects of temporarily reducing intraocular pressure a second group of embryos was prepared and studied exactly as above except that the indwelling glass tube was removed 24 hours after it had been introduced. In such cases the incision heals over and vitreous humor accumulates again. The cornea in these cases expands at a rate intermediate between that of the unoperated on eyes and that of the intubated eyes.

Control Eyes.—As a control for trauma and other nonspecific factors associated with the operation a series of embryonic eyes were fitted with solid glass rods of the same outside dimensions as the tubes and were observed in the same way as were the intubated eyes. Since the incision which was made to allow introduction of the glass rod was smaller than the outside diameter of the rod, a tight fit was effected between the rod and the edge of the incision. Vitreous humor did not escape, and intraocular pressure was maintained. The mean diameters of corneas in this group were not significantly different from normal at any postoperative age. In addition, histologic sections revealed no differences between corneas of the unoperated on group and the control group. Thus the results obtained cannot be ascribed to trauma or to other nonspecific factors.

Comment

The maintenance of harmonious size and shape relationships among the ocular components as development proceeds is due to the action of a number of factors. In addition, the types of factors operating in ocular morphogenesis may differ from stage to stage in development. Thus, at early stages in the chick the size relationship between the lens anlage and the optic cup appears to depend upon the area of contact between the expanding optic vesicle and the overlying ectoderm.[9] In amphibia, at a relatively later stage, the work of Harrison [10] and Ballard [11] suggests that appropriate size relationships between the lens and the optic cup are adjusted and maintained by an interaction of these eye parts. The nature of the interaction was not specified. Weiss and Amprino [5] have demonstrated that the adjustment of the size and shape of scleral cartilages to the size and shape of the developing globe is dependent on intraocular pressure. I have shown in a similar study that proper size and spatial relations among the sclera, choroid coat, pigmented epithelium, and neural retina are also dependent on vitreal pressure.

While the mode of action of each of the factors mentioned is not yet clear, it seems evident that different types of factors come into play during successive periods of ocular development. During those phases of development following the period of early inductions, the maintenance of harmonious size and shape relationships among the different ocular components may be explained in at least two ways. As suggested by Harrison and Ballard, the parts may influence the growth rates of each other in such a way as to maintain harmony of size. Alternatively, the growth rates of all parts may be under the influence of a common underlying factor, or complex of factors, that operates to insure harmonious growth.

Although the alternatives presented are not mutually exclusive, preliminary work has focused my attention on intraocular pressure as a possible common factor underlying the remarkable temporal correlation in the changes in size and shape among ocular parts. If intraocular pressure operates in this way, it is obvious that it must be capable of influencing, in the appropriate directions, the size and shape of each of the ocular parts involved. The sclera, the choroid, the pigmented epithelium, and the neural retina are moulded to a greater or lesser extent under the influence of the expanding vitreous. The present study places the cornea among those parts of the eye which are shaped, at least in part, by tangential forces arising from intraocular pressure.

Summary

Reduction of pressure in the vitreal chamber of the eye during its development leads to a decrease in the size (surface area) of the cornea. The cornea develops normally in operated on controls. This is interpreted as indicating that the normal expansion of the cornea during ontogeny is dependent, among other factors, on the tangential forces generated in the wall of the eye by an expanding vitreous body.

333 Cedar St. (11).

REFERENCES

1. Harrison, R. B.: Heteroplastic Transplantations of the Eye in Amblystoma, Anat. Rec. 31:299, 1925.

2. Twitty, V. C., and Schwind, J. L.: The Growth of Eyes and Limbs Transplanted Heteroplastically Between 2 Species of Amblystoma, J. Exper. Zool. 59:61-86, 1931.

3. Twitty, V. C.: Size-Controlling Factors, in Second Symposium on Development and Growth, Growth, Supp., pp. 109-120, 1940.

4. Twitty, V. C., and van Wagtendonk, W. J.: A Suggested Mechanism for the Regulation of Proportionate Growth, Supported by Quantitative Data on the Blood Nutrients, Growth 4:349-360, 1940.

5. Weiss, P., and Amprino, R.: The Effect of Mechanical Stress on the Differentiation of Scleral Cartilage in Vitro and in the Embryo, Growth 4:245-258, 1940.

6. Coulombre, A. J.: Correlations of Structural and Biochemical Changes in the Developing Retina of the Chick, Am. J. Anat. 96:153-189, 1955.

7. Coulombre, A. J.: The Role of Intraocular Pressure in the Development of the Chick Eye: I. Control of Eye Size, J. Exper. Zool., to be published.

8. Twitty, V. C.: Eye: An Analysis of Development, Philadelphia, W. B. Saunders Company, 1955.

9. McKeehan, M. S.: A Quantitative Study of Self-Differentiation of Transplanted Lens Primordia in the Chick, J. Exper. Zool. 126:157-175, 1954.

10. Harrison, R. G.: Correlation in the Development and Growth of the Eye Studied by Means of Heteroplastic Transplantation, Roux Arch. Entwick-mech. 120:1-55, 1929.

11. Ballard, W. W.: Mutual Size Regulation Between Eye-Ball and Lens in Amblystoma Studied by Means of Heteroplastic Transplantation, J. Exper. Zool. 81:261-285, 1939.

Fixation Patterns in Strabismic Amblyopia

PAUL J. HAUSER, M.D., Evanston, Ill., and HERMANN M. BURIAN, M.D., Iowa City

Introduction

Investigations into the nature of amblyopia ex anopsia and into the behavior of the amblyopic eye have aroused renewed interest during recent years. In 1952 Brock and Givner,[1] and somewhat later Jaffe and Brock,[2] reported on a test by means of which they attempted to show that many amblyopic eyes fixated eccentrically. This work has been widely cited, and some rather far-reaching conclusions have been drawn from it (Linksz[3]). However, to our knowledge no one has troubled actually to repeat this test and to determine its validity or limitations. We have, therefore, undertaken to do this and are presenting our findings in this paper.

Methods and Clinical Material

The test of Brock and Givner applies to patients with amblyopia the well-known fact that an after-image, produced in one eye, can be accurately localized by most subjects when the exposed eye is occluded and the contralateral, unexposed eye is used for fixation. In the test devised by Brock and Givner the subject is asked to occlude the amblyopic eye and to fixate a vertical filament of light with the sound eye from a distance of 4 ft. (120 cm.). After a 20- to 30-second exposure to this light the patient fixates a tangent scale placed at a distance of 6 ft. (180 cm.). The zero point of this scale, its center point, is encircled by three concentric circles delimiting 1, 2, and 3 degrees on the scale. If the sound eye has fixated the filament with the fovea, then the after-image will be seen to pass through the zero point of the tangent scale if the fovea now fixates this point. After it has been demonstrated that the sound eye can fixate both the light and the scale centrally, the after-image is reinforced by another exposure to the light. This normal eye is then occluded, and the amblyopic eye is called upon to fixate the zero mark on the tangent scale. The patient will be aware of the after-image and, if there is normal retinal correspondence and if the fovea of the amblyopic eye takes up fixation on the tangent scale at zero, the so-called "transferred" after-image will appear to pass through this central point. If an eccentric or parafoveal area takes up fixation, the after-image should reasonably appear laterally to the central fixation point.

Brock and Givner found that patients examined by this test could be grouped into three major categories: those who saw the after-image with the amblyopic eye centrally, those to whom it appeared at a measurable distance from the central fixation target, and those who were not aware of the after-image. Brock and Givner stated that, among 379 patients so examined, (1) 20% of all uniocular amblyopes fixated along the centrofoveal axis of the amblyopic eye on occlusion of the good eye, whereas (2) the great majority of uniocular amblyopes fixated eccentrically, and (3) 80% of the patients with alternating strabismus were incapable of what Brock and Givner called "transfer," while 75% of the patients with unilateral strabismus could "transfer."

We have executed the Brock-Givner test as described by these authors, but in addition we have also reversed the procedure

Received for publication July 13, 1956.

From the Department of Ophthalmology, College of Medicine, State University of Iowa.

This work was done during the tenure by one of us (P. J. H.) of a Heed Fellowship in Ocular Motility and was reported at the Meeting of the Midwestern Section of the Association for Research in Ophthalmology, Chicago, March 17, 1956.

in all patients examined by producing a vertical after-image in the amblyopic eye. With this after-image we investigated the capacity of the amblyopic eye for direct fixation on the tangent screen and studied the localization of the after-image when the contralateral, sound eye fixated.

Our series consisted of 25 patients with unilateral amblyopia, ranging in age from 6 to 30 years, the majority being 9 to 14 years old. The number of patients may seem small, but the findings were so definite that it appeared superfluous to extend the study to a larger group.

All patients had been given routine motility examinations in the clinic, and all were examined with the Troposcope, the diplopia test, and the routine after-image test to establish the state of their retinal correspondence.

Results

The 25 patients could be separated into five groups in accordance with their response to our tests (Table 1).

In the first group, comprising seven patients, the after-image was centered under all conditions of testing. The patients in this group had normal retinal correspondence, and their behavior in the tests indicated to us that they fixated foveally with either eye.

TABLE 1.—*Summary of Findings*

Group	Localization of After-Image	Cases, No.
I	Central when fixating with either eye, whether exposed or unexposed	7
II	Central when fixating with exposed eye; according to ARC* when fixating with unexposed eye	9
III	Central when fixating with exposed normal or amblyopic eye and when fixating with normal eye after exposure of amblyopic eye; eccentric when fixating with amblyopic eye after exposure of normal eye	4
IV	Eccentric when fixating with either eye, whether exposed or unexposed	
V	After-image not perceived with unexposed eye fixating	3
Total		25

*ARC, anomalous retinal correspondence.

The second group, nine patients with anomalous retinal correspondence, demonstrated one of the major reasons for lateral localization of the after-image with fixation by the unexposed eye. In all these patients the vertical after-image was centered on the tangent screen when the exposed eye fixated but it was displaced laterally according to the prevailing angle of anomaly when the

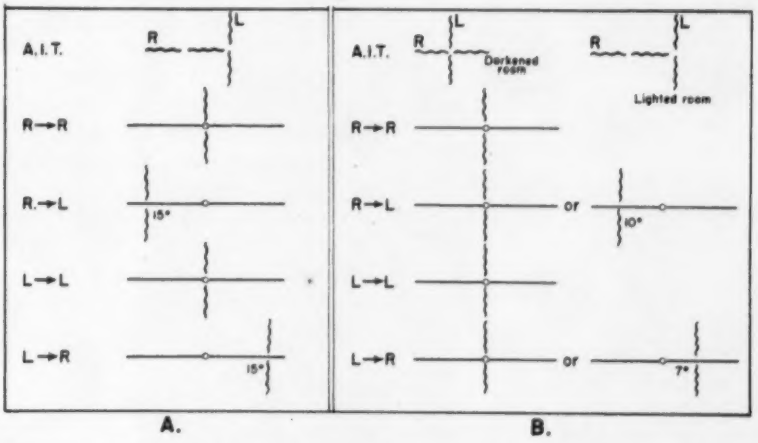


Fig. 1.—*A*, Case 15, 30-year-old woman with left esotropia; visual acuity: right eye 6/5, left eye 6/21. *B*, Case 12, 14-year-old boy with left esotropia; visual acuity: right eye 6/6, left eye 6/60. Examples of two typical cases of Group II. For explanation see text. A. I. T., after-image test. R→R, after-image produced in right eye, localized by right eye on tangent screen, with left eye occluded. R→L, after-image produced in right eye, localized by left eye on tangent screen with right eye occluded. L→L, L→R, analogous to R→R, R→L, but after-image produced in left eye.

contralateral eye fixated. Two typical examples are reproduced in Figure 1. Of these Case 12 is particularly interesting in that it represents a situation in which, owing to a labile anomalous correspondence, both a normal and an anomalous response could be elicited in the routine after-image test as well as in the Brock-Givner test.

Group III was made up of four patients who, when they fixated the tangent screen with their amblyopic eyes, responded with a slightly eccentric localization of the vertical after-image produced in their normal eyes.

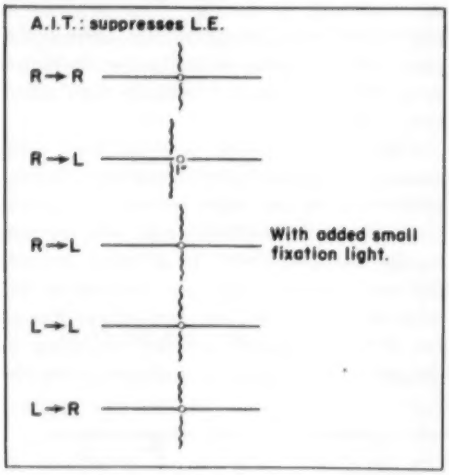


Fig. 2 (Case 18).—Left esotropia; visual acuity: right eye 6/6, left eye 3/60. Example of patient from Group III. Effect of adding fixation light to center of tangent screen. Abbreviations as in Figure 1.

This did, indeed, suggest eccentric fixation by these amblyopic eyes. However, when the vertical after-image was produced in the amblyopic eyes of these patients it appeared centered on the tangent screen both with fixation by the amblyopic eye and with fixation by the normal eye. Obviously, then, the amblyopic eye of these patients required a more adequate stimulus to central fixation than was offered by the central spot on the tangent screen. The after-image test light would seem to have provided such a stimulus.

The correctness of this conclusion was borne out by the following observation

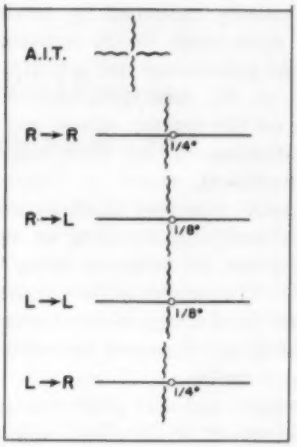


Fig. 3 (Case 26).—Eleven-year-old boy with right esotropia; visual acuity: right eye 6/60, left eye 6/6. Example of patient in Group IV. Abbreviations as in Figure 1.

(Fig. 2). One of the patients, while fixating the tangent scale with the amblyopic left eye, localized the vertical after-image produced in the normal right eye slightly to the left of the center. When a pinhole light was placed in the central fixation target, the patient immediately volunteered that the after-image had moved to pass through the center point. When the light was removed, the patient noted that the after-image was again lateral to the fixation target.

A peculiar situation obtained in the two patients of Group IV. These patients showed a slight eccentricity of the vertical after-image, regardless of whether they fixated with the exposed or unexposed eye and regardless of whether the eye was amblyopic or not (Fig. 3). Lastly, three patients (Group V) were never able to perceive the after-image when they fixated with the unexposed eye.

The distribution of the visual acuities and the state of the retinal correspondence of all 25 patients are presented in Table 2.

Comment

The ability for steady central fixation is not likely to be as good in an eye with reduced visual acuity as it is in an eye with standard vision, or better than standard

TABLE 2.—*Distribution of Visual Acuity and State of Retinal Correspondence*

Group*		Visual Acuity									Retinal Correspondence	
											Normal	Anomalous
I	R.E.	6/21	6/9	6/6	6/9	6/21	6/6	6/6			7	0
	L.E.	6/6	6/15	6/20	6/6	6/6	6/21	6/60				
II	R.E.	6/6	6/9	6/6	6/6	6/9	6/5	6/6	6/60	6/6	0	9
	L.E.	6/9	6/6	6/8	6/60	6/6	6/21	6/21	6/6	6/60		
III	R.E.	6/9	6/6	6/6	6/12						4	0
	L.E.	6/6	6/60	3/60	6/6							
IV	R.E.	6/6	6/60								2	0
	L.E.	6/60	6/6									
V	R.E.	6/6	6/9	6/12							1	2(?)
	L.E.	6/60	2/60	6/60								

* Patients divided according to groups listed in Table 1.

vision. One should, therefore, expect eyes with strabismic amblyopia not to fixate as well as do their fellow eyes. This is, indeed, sometimes the case, but gross defects of fixation are relatively rare, if one disregards so-called eccentric fixation, which is not considered in this paper.

A closer study of the fixation pattern of amblyopic eyes is desirable, and new methods developed for this specific purpose would be welcome. Unfortunately, the method advocated by Brock and Givner has proved to be disappointing. In our series of 25 patients, 7 reported central fixation under all conditions of testing. In nine patients there was central fixation when the exposed eye was used and a gross deviation, corresponding to the angle of anomaly of the patients, when the unexposed eye fixated. Anomalous correspondence was thus an important limiting factor in the applicability of the test.

The findings in this second group of cases agree with those of Hansen,[4] who could not confirm the claim of Jaffe[5] that patients with anomalous retinal correspondence are not aware of a vertical after-image when the stimulated eye is occluded. This test gives, therefore, no evidence for a lack of integration of the eyes in anomalous retinal correspondence. It gives, on the contrary, very good evidence, if such is still needed, for the fact that anomalous correspondence is demonstrable only in binocular vision and should not be confused with anomalies of central fixation. In our patients, whenever the stimulated eye was called upon to fixate alone the after-image passed through the fixation point; when the unexposed eye fixated on the tangent screen, the stimulation, persisting in the occluded fellow eye, was integrated into the visual field and localized anomalously.

Most important for the evaluation of the Brock-Givner test were the patients in the third group, who responded in the same manner as the majority of the patients tested by Brock and Givner. It could be shown, however, that this response was not due to an absolute inability of these eyes for central fixation; if the stimulus was adequate, they fixated centrally. But these eyes did require a stronger stimulus to bring about central fixation than did the normal fellow eye. It is entirely conceivable that there exists a gradation in the ability for central fixation of amblyopic eyes. At one end of the scale would be the amblyopic eyes with full ability to fixate centrally—at the other end those who altogether lack this ability, as in so-called eccentric fixation.

It must also be kept in mind that several additional factors need to be considered. A particularly important item is the matter of attention. Attention to fixation is critical in relating an after-image to a fixation target. The slightest lapse in attention brings about a marked shift of the after-image. Also, some persons are more responsive than others to the production of after-images. Several alert, normal adults to whom we gave the test experienced difficulties in visualizing the after-image when the ex-

posed eye was occluded. It did not always appear immediately or would fade out for brief periods, making its localization somewhat uncertain. It is by these difficulties and by lack of attention that we explain the baffling findings in Group IV of our patients and the absence of an awareness of the after-image in the three patients of Group V, one of whom was a mentally retarded boy 12 years of age.

The net result of our study is that it has shown to us that relatively potent stimuli are required in some instances to make the amblyopic eye fixate centrally. But neither the test of Brock and Givner nor our modification of this test permits one to draw conclusions about the fixation pattern in amblyopia ex anopsia, let alone about the nature of the condition. One can not decide on the basis of these tests whether amblyopia ex anopsia is primarily a sensory anomaly or primarily an abnormality of the motor function, as has been claimed (Linksz[3]). To elucidate this problem, and similar ones, considerably more refined methods of investigation are required than have hitherto been employed.

Summary

The test advocated by Brock and Givner for the study of the fixation pattern in patients with amblyopia ex anopsia has been expanded and has been given to 25 patients. In contrast to the earlier authors, we did not find that this test gave evidence that the majority of patients fixated eccentrically with their amblyopic eye. We did, however, find that some patients required a stronger stimulus to be made to fixate centrally with their amblyopic eye than was required for the normal fellow eye. Anomalous retinal correspondence and wandering of attention place definite limitations on the applicability of the test.

636 Church St. (Dr. Hauser).
University Hospitals (Dr. Burian).

REFERENCES

1. Brock, F. W., and Givner, I.: Fixation Anomalies in Amblyopia, A. M. A. Arch. Ophth. 47: 775-786, 1952.

2. Jaffe, N. S., and Brock, F. W.: Some Phenomena Associated with Amblyopia, Am. J. Ophth. 36:1075-1086, 1953.

3. Linksz, A.: Physiology of the Eye, New York, Grune & Stratton, Inc., 1952, Vol. 2. Vision.

4. Hansen, A. K.: "After-Image Transfer Test" in Anomalous Retinal Correspondence, A. M. A. Arch. Ophth. 52:369-374, 1954.

5. Jaffe, N. S.: Anomalous Projection, Am. J. Ophth. 36:829-838, 1953.

The Hyperbolas of Accommodation and Convergence

ROBERT V. HILL, M.D., Longview, Wash.

It would be highly desirable to have a mathematical analysis of the normal functions and interrelationships of accommodation and convergence. These two functions seem to behave mathematically, i. e., they follow with absolute constancy (of unit measure) certain predetermined patterns; therefore, with a "physiologically ideal" relationship between his accommodation and convergence, for a given patient there can be only one mathematically correct value for each function. Although this would seem obvious, I have been unable to find a specific treatise on these mathematical identities and interrelationships. The probable reason is that accommodation has been treated as an algebraic and convergence as a nonalgebraic function. Using constant units of measurement it is impossible to express in a simple equation the coordinate roles of an algebraic function (accommodation) and a transcendental or nonalgebraic function (convergence).

It is my purpose to describe how this problem can be solved by changing the transcendental function of convergence to an algebraic one. This is done simply by using a noncircular and inconstant unit of measurement, the prism diopter. It will be shown that this is mathematically expedient and accurate within physiologically attainable limits.

A brief discussion of the relative merits of the most commonly used units of convergence measurement will help to provide a basis for a logical approach to this problem. The term "meter angle" has no mathematical significance and merits no discussion, except to suggest that it may have been partly responsible for blocking progress in an adequate mathematical analysis of the convergence function. The terms degree and radian are mathematically correct because of their constancy of unit value, but they have the disadvantages of requiring the use of an inverse trigonometric formula * and trigonometric function tables for determinations of the coordinate convergence requirement in either of these terms. Also, there is no rationally resolvable mathematical relationship of this transcendental function (in focal diopters of convergence) to the algebraic function of accommodation. It is, therefore, desirable to use a unit value of convergence, of sufficient accuracy within attainable physiologic limits, of sufficient familiarity to ophthalmologists, and whose unit value allows a mathematically exact correlation, preferably a rational, integral expression, of convergence to accommodation. Such a unit is the prism diopter, and with this unit, and this unit only, the convergence function becomes, mathematically, a true hyperbola,† of exactly the same type as that of accommodation.

The convergence and accommodation functions are, in prism diopters and focal diopters, respectively, now of the same mathematical order. In fact, they are of the special type of hyperbola called equilateral or rectangular, so-called because of their asymptotes,‡ which are at right angles to each other. It is now convenient to use these asymptotes as the x- and y- (abscissae and ordinates) axes in the conventional rectangular coordinate system of plotting curves. It is even more convenient to super-

Received for publication Aug. 31, 1956.

From the Department of Ophthalmology, University of Oregon Medical School.

Read before the Western Section of the Association for Research in Ophthalmology, San Francisco, Feb. 7, 1956.

* See Appendix B.

† See Appendix B.

‡ See Appendix B.

impose the convergence and accommodation curves, with the common, independent variable as focal distance in meters on the x-axis, because each is an equilateral hyperbola. (It is mathematically conventional to represent the independent variable on the x-axis).§ The convergence and accommodation equilateral hyperbolas differ only by a constant, the interpupillary distance, and representative values of this difference in different persons may be plotted in separate columns beside the y-axis. We now have the mathematical relationships of convergence and accommodation to each other and each to a common third independent variable (sometimes called a parameter) in both graph and equation form (Fig. 1). Thus, a single point on these superimposed curves determines the exact coordinate values in all three variables. Derivation of the hyperbolic and parametric equations is presented in Appendix B.

It is now possible to discuss some of the mathematical, physiological, and clinical implications of this analysis. The outstanding features of the mathematical analysis are the following: (1) both convergence and accommodation have identical and unique solutions (i. e., equilateral hyperbolas) when convergence is measured in prism diopter units; (2) the transcendental curve, using degrees or radian units of measurement, is identical to the algebraic curve (hyperbola, in this instance), using the prism diopter unit of measurement, up to 5 focal diopters (or ⅕ meters). They diverge a physiologically insignificant amount (Fig. 2) even at 7 focal diopters (or ⅐ meters); (3) the convergence and accommodation curves are identical power law functions‖ (Fig. 1); thus great changes in focal distance at great distances from the eyes cause only slight (and proportionate) changes in accommodation and convergence requirements, whereas very small changes in focal distances very close to the eyes cause very large (and proportionate) changes in accommodation and convergence requirements¶; (4) the

§ See Appendix B.

‖ See Appendix B.

¶ This is easily determined by observation of the relative "slope of the curve" at different points along the x-axis. By elementary differential calculus, this slope, at any point tangent to the curve, can be proved to represent the "exact rate of change" of the y-values per unit change of x-values. Further discussion of the use and limitations of calculus to these equations will be presented in a subsequent paper.

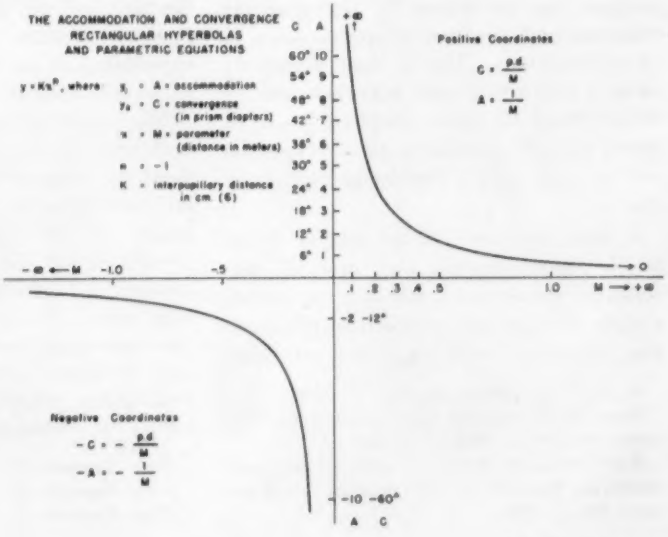


Fig. 1.—The superimposed hyperbolas of accommodation and convergence facilitate the mathematical analysis of these functions.

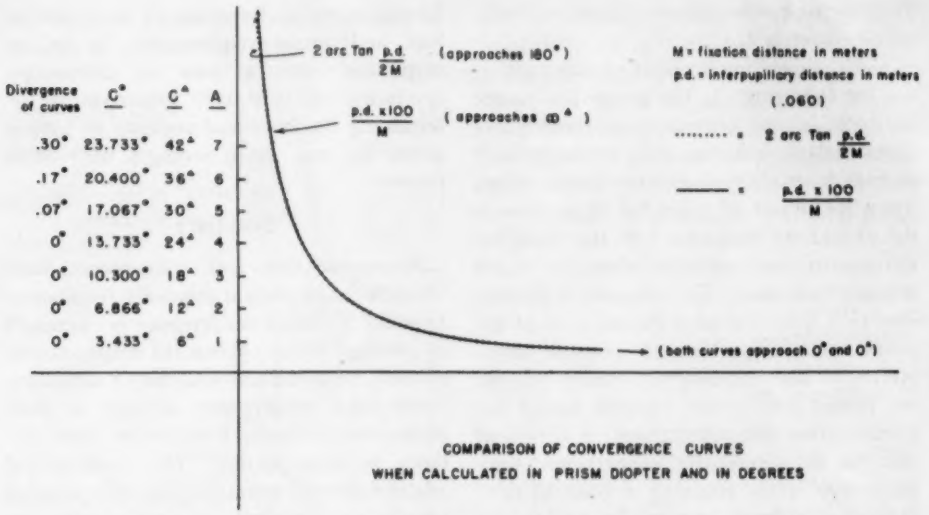

2 arc Tan p.d. / 2M (approaches 180°)
p.d. x100 / M (approaches ∞ Δ)
M = fixation distance in meters
p.d. = interpupillary distance in meters
(.060)
..... = 2 arc Tan p.d. / 2M
——— = p.d. x 100 / M
Divergence of curves
C° C Δ A
.30° 23.733° 42Δ 7
.17° 20.400° 36Δ 6
.07° 17.067° 30Δ 5
0° 13.733° 24Δ 4
0° 10.300° 18Δ 3
0° 6.866° 12Δ 2
0° 3.433° 6Δ 1
(both curves approach 0° and 0°)
COMPARISON OF CONVERGENCE CURVES
WHEN CALCULATED IN PRISM DIOPTER AND IN DEGREES

Fig. 2.—The convergence curves, even when plotted separately as transcendental and algebraic functions, retain numerical identity within physiologically significant limits.

variables, accommodation and convergence, have a common third variable, focal distance, which, when eliminated parametrically,# gives the "straight line curve"* coordinate relationship of accommodation to convergence. This is an alternate method of deriving the convergence to accommodation relationship which was presented in a recent paper[3]; (5) a single point on the superimposed hyperbolas (either on rectangular coordinate or log graph paper) represents the mathematically ideal physiologic coordinate requirement for accommodation and convergence at any focal distance.

Some physiologic implications of this mathematical analysis are the following: (1) a proper reference point is established without which no deviation (or "dissociations") of accommodation relative to convergence or convergence relative to fixation distance can be adequately measured and discussed. This includes variations, even though slight, in so-called normal, bifoveal vision, as for example in fixation disparity. In fact, the measurements of fixation disparity limits have not been described with reference to the mathematically calculated "ideal physiologic zero point," although such a reference point is much more desirable than the less accurate physiologically subjective determinations previously made for such a point; (2) the ideal reference point for convergence (point of intersection of the visual axes) is determined mathematically and not by statistical averages of subjective responses. It therefore provides an unequivocal standard, for any patient, in whom it is desired to make any quantitative analysis of the physiologic acts of "dissociation" of any of these three variables (accommodation, convergence, and fixation distance) with respect to one or both of the others; (3) the negative halves of the superimposed accommodation and convergence hyperbolas (Fig. 1) provides an equally accurate reference point for the theoretical coordinate requirements of accommodation and convergence at focal distances "beyond infinity," as for example in an uncorrected

See Appendix B.

* The graph of an equilateral hyperbola would be represented as a straight line on logarithmic graph paper, but this is not considered desirable at this point because it would not be readily differentiable from any other power law function, since all are straight lines in log graph form.

hypermetrope who relaxes his accommodation completely.†

Some clinical implications of this analysis are the following: 1. The power law nature of both accommodation and convergence (hyperbolas) indicates the extremely large necessary changes of accommodative effort, when the object of regard is very close to the patient, as compared with the negligible changes of such stimulus when the object is many feet away. This suggests a possible clue to a more complete explanation of the common clinical problem of "accommodative esotropia" and "convergence excess." From the power law curves (hyperbolas of accommodation and convergence) it is evident that the accommodative convergence stimulus, even when retaining a "one to one" ratio of stimulus to response,[2] must increase extremely rapidly in the short ranges of fixation distance.‡ Now if an increased "convergence tonus," for example in an uncorrected hypermetrope, is added to these normally extremely rapid accommodation and convergent requirement changes within these short ranges, an even greater impetus is added to the already rapidly increasing convergence stimulus (by accommodation). 2. Apologies for use of the prism diopter unit of measurement are not in order, since it is the most desirable, even for mathematical reasons. 3. The "dioptric coordinate"[2,3] system (that is, prism diopters of convergence and focal diopters of accommodation, plotted and equated coordinately—i. e., in conventional rectangular coordinates) presents a method of rapid determination of each physiologically ideal requirement with respect to the other and with respect to focal or fixation distance. This is essential, for example, in calculating lens and prism requirements to be incorporated into a pair of orthoscopic spectacles. It is equally important in determining the fractional amounts of base in prism for any given strength of reading lenses.

† A discussion of "negative coordinates" and their physiological and clinical applications will be presented at a later date (also, see Appendix B).

‡ This is evident by "slope changes" per unit fixation distance or, more exactly, by differential calculus, from which these slope changes are found to vary as the square of the fixation distance, e. g., differentiating the accommodation hyperbola, $A=1/M$, $dA/dM=-1/M^2$, where $A=$ accommodation in focal diopters and M=fixation distance in meters.

Summary

Accommodation and convergence have identical mathematical solutions (equilateral hyperbolas) when convergence is expressed in prism diopters. When the prism diopter is used, mathematical analysis of accommodation and convergence, relative to their parametric variable, fixation or focal distance, becomes possible. This mathematical analysis permits a conventional (rectangular coordinate) method of presenting the "physiologically ideal" relationship of accommodation and convergence with respect to their common third variable, fixation distance. A few mathematical, physiologic, and clinical advantages of the accommodation and convergence hyperbolas are discussed.

Appendix A

The mathematical relationships between prism diopter and circular function (radians or degrees) measurements may be compared in the following manner. The half angle method of trigonometric derivation of convergence angle on the midline gives

$\phi=2$ arc tan P. D./$2M$

where

M=distance from the midpoint on the base line (an imaginary line between the centers of rotation of each eye) at any point from 0 to infinity, perpendicular to the base line, and measured in meters

ϕ=convergent angle at the point of intersection of the visual axes

P. D.=interpupillary distance in meters.§

The range of M is from ∞ to 0; therefore, from the formula, the range for ϕ is 0 to

§ P. D. is used in preference to the inter-rotational center distance because it is a familiar term and is practically identical to the inter-rotational distance when measured with the eyes in the primary position.

180 degrees. The half angle method of derivation is as follows (Fig. 3):

$$\tan \theta = \frac{1}{2} \text{P. D.}/M \qquad (1)$$

therefore

$$\theta = \text{arc tan P. D.}/2M, \text{ and} \qquad (2)$$
$$\phi = 2\theta = 2 \text{ arc tan P. D.}/2M \qquad (3)$$

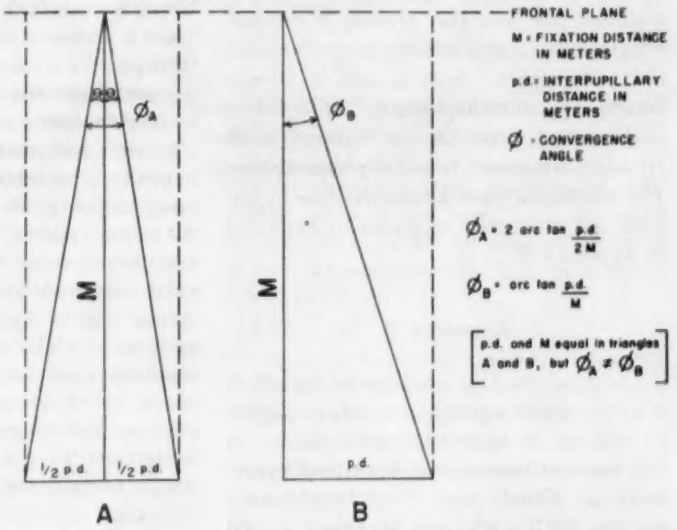


Fig. 3.—Trigonometric solutions of the convergent angle are inconstant, even at a constant frontal plane distance, depending on laterality of fixation on this plane.

On the other hand, the convergence formula for either visual axis crossing over to intersect the other, which remains in the primary position, gives considerably different values for short fixation distances, even though both are trigonometric functions and both are expressed in the constant unit value, degree. This formula is

$$\theta = \text{arc tan P. D.}/M$$

The range of M is again from ∞ to 0, but (from the formula) the range of θ is now from 0 to 90 degrees. The derivation of this formula is as follows:

$$\tan \theta = \text{P. D.}/M \qquad (1)$$

therefore

$$\theta = \text{arc tan P. D.}/M \qquad (2)$$

It should now be evident that even with precise trigonometric methods and with units of measurement of constant value, no single formula can, in absolute values, express the convergence of the visual axes within the normal physiologic limits of conjugate gaze from the midline. In other words, for absolute accuracy of measurement of the convergent angle at any fixation distance from the eyes, separate calculations for an infinitely large number of triangles, whose apices would be represented by an infinitely large number of points on a frontal plane, would be necessary. In addition to this difficulty, there is the problem of making an infinitely large number of separate calculations for the distance of each eye to the fixation point in order to express (with mathematical accuracy) the relationship of accommodation to convergence for each of these infinitely large numbers of geometrical situations.

The problems of mathematical calculation mentioned above have no real physiologic significance, however, since they are of importance only in the extremely short ranges of fixation and focal distances (20 cm. or less). On the other hand, the prism diopter unit of convergence measurement, which causes no such mathematical problems at any fixation distance, retains absolute constancy of unit value up to this range (Fig. 2), and even up to 7 D. of accommodation ($\frac{1}{7}$ meter fixation distance)

there is only 0.3 degrees of difference when calculated by the trigonometric method ($\phi=2$ arc tan P. D./$2M$), as compared with the prism diopter (convergence hyperbola) method. It is therefore desirable, from the standpoint of mathematical convenience as well as accuracy (within the limits just mentioned), to use a unit value of convergence which will not only avoid the mathematical impasses but will also provide a rational, integral relationship between accommodation and convergence. Such a unit is already known to ophthalmologists, but its true mathematical value has not received much (if any) attention. It is the prism diopter. The convergence and accommodation hyperbolas and parametric equations are described in Appendix B.

Appendix B

The equilateral or rectangular hyperbola is a very useful algebraic formula in applied as well as in theoretical mathematics. A few common examples of equilateral hyperbolas are Ohm's law ($1=E/R$), Boyle's gas law ($PV=K$), and Newton's second law of motion ($F=ma$). A brief review of some important features of hyperbolas is considered desirable for those who may have forgotten their college algebra.

The hyperbola is an algebraic equation whose curve is defined as the locus of a point which moves in a plane in such a way that the difference of its distances from two fixed points is constant. It has two symmetrical branches, when plotted in the mathematically conventional rectangular coordinate system. The general form equation is

$$x^2/a^2-y^2/b^2=1$$

where

x and y=the independent and dependent variables, respectively

a=the semitransverse axis distance

b=the semiconjugate axis distance.

The asymptotes ‖ of the hyperbola intersect at a point on the transverse axis midway between the vertices of the two curves, i. e., a distance, a, from each vertex. The angle of intersection here determines the shape of the hyperbola. This angle is most easily determined by the eccentricity, c/a, where c is the semifocus distance and a is the semitransverse axis distance. (In the equilateral hyperbola this ratio is always $\sqrt{2}$, or 1.414.) When this angle of intersection is 90 degrees, i. e., the asymptotes are mutually perpendicular, the hyperbola is said to be rectangular or equilateral. Now, for the sake of mathematical convenience, these mutually perpendicular asymptotes are rotated clockwise or counterclockwise about the origin (midway on the transverse axis), and they become the conventional rectangular coordinate axes. The formula for this special type of hyperbola is derived in the same manner (by analytic geometry) as the standard form and, when simplified, becomes $xy=k$ where x and y are the independent and dependent variables, respectively, and k is a constant. Solving this simple formula for $f(x)$, we find

$$y=k/x$$

The formula $y=k/x$, which expresses the reciprocal function of one variable to another, is also a power law function. This is evident by comparing it to the standard form of the power law equation, $y=kx^n$, where n is the exponent, $\neq 0$. Letting $n=-1$ in this equation gives $y=k/x$, the standard form for the equilateral hyperbola. By definition, accommodation varies inversely as the distance (in meters) from a point to the eye, or, by symbols, $A=1/M$, where A (accommodation in focal diopters) is the dependent variable and M (in meters) is the independent variable. It is, therefore, also an equilateral hyperbola ($y=k/x$) and a

‖ An asymptote is a straight line which is related to a curve in such a way that as a variable point moves along the curve further and further from the origin its distance from this line continually decreases and approaches 0 as a limit when the distance of the point from the origin becomes infinite.

power law function ($y=kx^n$) when $n=-1$. By using the prism diopter unit of convergence, the formula for convergence ($C=A\times$P. D.$=$P. D.$/M$) is also an equilateral hyperbola and power law function, identical to that of accommodation except for the value of the constant k, where the P. D. is expressed in centimeters, or P. D.$\times 100$ with P. D. expressed in meters. The geometric derivation of this formula was presented in the 1955 *American Orthoptic Journal*.[3] The accommodation hyperbola is represented graphically in Figure 1 by the ordinate values (positive and negative) under A, and by M on the abscissa (positive and negative). The convergence hyperbola is represented by the ordinate values under Column C, and by M on the abscissa. The two curves are superimposed because they are mathematically identical, and a single point on the curve facilitates the determination of the coordinate values of all three variables. It will be noted that one half of the hyperbola represents all positive values of x and y and the other represents all negative values. The negative distance, $-M$, on the x-axis has the same meaning as the imaginary focal point behind the hypermetropic eye. The negative, $-A$, ordinate (y-axis) values indicate the corresponding hypermetropic dioptric distances.

Example: A+3.00 D. hypermetrope may relax accommodation from any real, physiologically attainable value, say 1 meter (where he is using 4 D. accommodation) through plus infinity (where he is using 3 D. accommodation) to minus infinity (where he is still using 3 D. accommodation) to $-\frac{1}{3}$ M (where his accommodation becomes zero.) The -3 D. coordinate in this case thus indicates the amount of accommodation which can be relaxed "beyond infinity" and may be called "negative accommodation," since it is on the negative half of the hyperbola. This should not be confused with relaxation of accommodation on the positive half of the curve. Negative accommodation in this sense is only possible for hypermetropes.

We now have two equilateral hyperbolas each of which has a variable which is common to both equations. It is fixation distance, M. This is called a parameter, and if a direct relation of accommodation to convergence is desired, it may be eliminated as follows:

$$A=1/M \qquad (1)$$

$$C=\text{P. D.}/M \qquad (2)$$

When equation (1) is multiplied with the value P. D., it becomes

$$A\times\text{P. D.}=\text{P. D.}/M$$

and is, therefore, equal to equation (2). Things equal to the same thing are equal to each other, mathematically, and equating (1) to (2) parametrically, i. e., by eliminating P. D.$/M$,

$$A\times\text{P. D.}=C$$

where C is expressed in prism diopters, P. D. is in centimeters, and A is focal diopters for an emmetropic patient. It is now evident from the above parametric relationships that each dependent variable (accommodation and convergence) may be solved directly if the value of the other is known. Therefore, either function may become the independent variable as the other becomes the dependent variable.

Dr. William Bruce, Ph.D., Professor of Mathematics, Lower Columbia Junior College, Longview, Wash., gave inspiration and assistance in the preparation of this manuscript.

1329 Broadway.

REFERENCES

1. Smail, L. L.: Analytic Geometry and Calculus, New York, Appleton-Century-Crofts Company, Inc., 1953.

2. Hill, R. V.: The Accommodative Effort Syndrome: Pathologic Physiology, Am. J. Ophth. 34:423-431, 1951.

3. Hill, R. V.: A Simple Method of Determining the Coordinate Requirements of Convergence, Am. Orthop. J. 5:105-108, 1955.

Studies on the Glutathione in Bovine Lens

JIN H. KINOSHITA, Ph.D., and THOMAS MASURAT, B.A., Boston

Introduction

Many investigators have reported on the presence of glutathione (GSH) in lens.[1] Glutathione has been suspected of serving some important functions in the physiology of the lens, since one of the first observable changes in experimental cataract formation is a marked decrease in GSH concentration. The reason for the presence of the unusually high concentrations of GSH has never been adequately explained. It has been definitely established that one of the factors contributing to the presence of this tripeptide is that the lens is capable of its synthesis. The incorporation of radioactive glycine into the glutathione molecule was demonstrated to occur in the lens by Kinsey and Merriam.[2] Recently, GSH synthesis from its component amino acids in lens homogenates was observed by Daisley.[3]

However, other factors leading to the accumulation of this tripeptide have not been thoroughly studied. The present paper is an attempt in this direction and reports a study on the various factors which may influence the state of GSH in lens. It is divided into three sections: (I) the possible relationship between glutathione and carbohydrate metabolism, (II) the peptidase activity of lens, (III) the extractability of glutathione from the lens.

Methods

Many of the methods, experimental procedures and materials employed have been described in previous reports.[4-7] Radioactive assays were made with a Geiger gas-flow counter rather than the end-window counter used in previous studies. The phosphate buffer employed in the C^{14} glucose study was composed of 0.04 M NaK phosphate buffer, pH 7.5; 0.08 M NaCl, and 0.005 M $MgSO_4$.

In the peptidase studies, glycine was measured on trichloracetic acid filtrates by the method of Alexander et al.[8] Peptidase activity was determined by the procedures described by Schwarz and Engel.[9] The extent of glutathione hydrolysis was followed by the amount of cysteinylglycine released, with use of the Sullivan-Hess method.[10,11] Cysteinylglycine was prepared from glutathione;[12] γ-glutamylglycine was synthesized by the method of King and Kidd,[13] and α-glutamyl glutamate was supplied by Dr. E. G. Ball. All other peptides used were obtained commercially. The following procedures were employed to separate the leucylglycine and glycylleucine dipeptidases. Bovine lens was homogenized in a Waring Blendor for three minutes with 10 volumes of cold distilled water. The homogenate was centrifuged at 1500 rpm in a No. 1 International centrifuge for 10 minutes, and the precipitate recovered was discarded. The resulting supernatant fluid was chilled in an ice bath, and solid ammonium sulfate was added until the lens homogenate was 30% saturated with respect to the ammonium sulfate concentration. The mixture was centrifuged in a Servall centrifuge at 8 C, and the precipitate recovered was discarded. The ammonium sulfate concentration of the supernatant fluid was then raised to 40% saturation by the addition of solid ammonium sulfate. The precipitate recovered after centrifugation was the 30%-40% fraction. Ammonium sulfate concentration of the supernatant fluid was then raised to 60%, and the precipitate which resulted was the 40%-60% fraction. Each fraction was dissolved in a volume of water one-fifth that of the original lens homogenate. The fractions were dialyzed overnight at 8 C against 100 volumes of water to remove the excess ammonium sulfate. A volume of 10 ml. of the 40%-60% fraction was treated with 4 ml. of calcium phosphate gel which contained 1.3 gm/ml. of calcium phosphate.[14] After centrifugation, the leucylglycine dipeptidase was eluted from the gel with 5 ml. of 0.1 M Na_2HPO_4 solution.

In the glutathione extraction studies, bovine lens, the weight of which was determined on a torsion balance, was incubated in 10 ml. of buffer contained in an Erlenmeyer flask and shaken in a

Received for publication Sept. 4, 1956.

This project was supported by the Atomic Energy Commission.

From the Howe Laboratory of Ophthalmology Harvard Medical School and Massachusetts Eye and Ear Infirmary.

water bath at 38 C. The hypertonic phosphate buffer employed in this study was made up of 0.1 M phosphate buffer, pH 7.4, and 0.16 M NaCl. The isotonic buffer contained 0.06 M phosphate buffer, pH 7.4, and 0.072 M NaCl. The hypotonic phosphate buffer was made by taking one volume of the isotonic buffer and one volume of water. After the incubation, the lens was removed, rinsed in distilled water, and placed in a 25 ml. graduated test tube. It was homogenized in 8 ml. of 10% sulfosalicylic acid (SSA). The volume was made up to 20 ml. with distilled water and then filtered. The incubating medium was quantitatively transferred from the flask to a 25 ml. graduated tube, acidified with 5 ml. of 10% SSA, and made up to a volume of 20 ml. with water. Glutathione was determined on these acid filtrates by the nitroprusside test.[35] Oxidized glutathione was electrolytically reduced, with use of the conditions described by Dohan and Woodward,[36] with the modifications of Bhattacharya et al.[37] The amount of glutathione in the oxidized form was taken as the difference between the values obtained before and after electrolytic reduction. As a check of this method, known amounts of oxidized glutathione were added to SSA filtrates of lens, and the recovery observed was always above 96%.

Results and Comment

Section I. The Possible Relationship Between Glutathione and Carbohydrate Metabolism.—In a previous paper[6] evidence suggested that in lens carbon dioxide produced from glucose metabolism may proceed by way of the shunt mechanism. It was also pointed out that the reoxidation of reduced triphosphopyridine nucleotide (TPNH) formed in the direct oxidation of glucose-6-phosphate may not necessarily involve the cytochrome system. As a working hypothesis, the GSH-ascorbic acid oxidative system was proposed as a possible alternate electron acceptor system in lens. The evidence for the first step of this scheme was the demonstration that the enzyme, GSH reductase, is able to catalyze the interaction of TPNH and oxidized glutathione (GSSG). In lens homogenates, it was shown that the dehydrogenases of the shunt pathway can be coupled with GSH reductase. This reaction can serve as a possible mechanism by which sufficient quantities of TPN in the oxidized form are available for use in the direct oxidative pathway. Since there is a small amount of GSSG found in lens, some mechanism must also exist which is capable of oxidizing glutathione. Further study is needed to elucidate this process.

The participation of the GSH reductase was suggested by the observation that when lens is incubated in presence of GSSG a stimulation in the oxidation of carbon-1 (C-1) of glucose by 88% results.[6] However, further study has revealed that this large stimulation is only observed when lens is incubated in phosphate buffer. As shown in Table 1, GSSG caused only a slight stimulation of C-1 oxidation of glucose when Krebs-Ringer solution was the buffer employed and had no effect when bovine aqueous humor was used. The explanation may be that in phosphate buffer the reoxidation of TPNH is not as rapid as its formation by the dehydrogenases of the shunt mechanism. Therefore, in this case, the excess GSSG increased the C-1 oxidation of glucose by stimulating the reoxidation of TPNH. In the other buffers, the oxidation

TABLE 1.—*Oxidation of 1-C^{14} Glucose by Bovine Lens* *

State of Lens	Buffer	No. Obs.	GSSG, μM/Ml.	Cpm Recovered as $C^{14}O_2$ ± S.E.
Normal	Phosphate	8	0	405±22
Normal	Phosphate	8	10	732±51
Normal	Krebs-Ringer	8	0	672±25
Normal	Krebs-Ringer	8	10	715±22
Normal	Aqueous humor	4	0	740±21
Normal	Aqueous humor	4	10	745±28
Preincubated	Aqueous humor	4	0	680±20
Preincubated	Aqueous humor	2	10	695±15
Preincubated with 10 mg. NEM	Aqueous humor	4	0	70±13
Preincubated with 10 mg. NEM	Aqueous humor	4	10	172±14
Preincubated with 10 mg. NEM	Aqueous humor	4	(GSH) 20	134±18

*Bovine lens was incubated in 8.0 ml. of buffer containing 20μM/ml. of 1-C^{14} glucose, with a specific activity of 405 cpm/μM. The results are expressed as cpm/2 gm. wet weight/four hours. The preincubation of lens was for one hour in Krebs-Ringer buffer, after which the lens was transferred to the aqueous humor containing 1-C^{14} glucose.

of TPNH is not the rate-limiting step, and consequently the presence of excess GSSG does not influence the C-1 oxidation of glucose. As is shown in Table 1, this explanation is consistent with the observation that the presence of GSSG in phosphate buffer increases the amount of $C^{14}O_2$ produced so that it is equal to that observed in the other two buffers.

When aqueous humor was employed as the buffer, the presence of GSSG stimulated C-1 oxidation of glucose under one experimental condition. The observation was made on lens treated with N-ethylmaleimide (NEM), which is a compound known to combine irreversibly with sulfhydryl groups.[18] It was thought that if NEM would combine with GSH then the conversion of GSH to GSSG would be blocked, and, since only a small amount of the oxidized form is present, a need for GSSG would soon result. To approach this problem experimentally, lens was preincubated in 10 ml. of Krebs-Ringer buffer containing 10 mg. of NEM. After one hour the lens was transferred to a flask containing aqueous humor with added 1-C^{14} glucose and incubated for an additional four hours. As the results indicate (Table 1), the rate of C-1 oxidation to $C^{14}O_2$ was markedly reduced. The NEM-treated lens yielded only 70 cpm of $C^{14}O_2$ while the control lens, similarly preincubated in Krebs-Ringer buffer without NEM, oxidized glucose to produce 680 cpm of $C^{14}O_2$. The addition of either glutathione or GSSG in the aqueous humor increased the C-1 oxidation of glucose by the NEM-treated lens. Since it was shown in this study that the GSH is rapidly oxidized in aqueous humor, the observed increase in C-1 oxidation must be due to the GSSG. The presence of GSSG did not increase the oxidation to values obtained by the control lens. Apparently the action of NEM was not restricted to combining with GSH but also inhibited essential enzymes by reacting with their sulfhydryl groups. It was shown in these lenses treated with NEM that a 50%-60% drop in glutathione concentration occurred. It may appear somewhat surprising that such a large inhibition in the C-1 oxidation was observed when a considerable amount of GSH was still detectable in lens. However, as indicated in the findings of Section III, most of the glutathione is bound in some manner so that it may not be easily converted to the oxidized form.

The activity of glutathione reductase in lens was next determined to establish whether it is sufficiently active to carry out the proposed oxidative function. Two methods were employed in this study. At 38 C, the method of Rall and Lenhninger[19] indicated that 4.4 micromoles (μM) of GSSG were reduced (or TPNH oxidized) per hour by 1 gm. (wet) of dialyzed bovine lens homogenate. The GSH reductase activity was also measured by following the reduction of TPNH spectrophotometrically, with use of the conditions employed by van Heyningen and Pirie.[20] By this method, the GSH reductase activity was 1.7μM/gm/hour at 25 C. From these results it appears that the Q_{10} of the reaction is about 2.2. The GSH reductase activity observed in these studies is in fair agreement with that observed by van Heyningen and Pirie.[20]

From the oxidation of C-1 of glucose in aqueous humor (Table 1), it can be calculated that about 0.2μM/gm/hour of glucose is oxidized via the shunt mechanism. Since in this pathway for each mole of carbon dioxide produced there are two reactions which yield reduced TPN, the rate of production of TPNH is 0.4μM/gm/hour. It would appear, therefore, that the GSH reductase activity of 4.4μM/gm/hour is sufficiently active to serve as the mechanism for the reoxidation of the coenzyme.

It may be noteworthy that the enzymes of the shunt mechanism and GSH reductase are found in the same fraction of the cell—that is, in the soluble cytoplasm. This suggests the possibility of the interaction of these enzymes in other tissues as well as in lens. Since TPN is present in small quantities in most tissues, it would seem advantageous for the oxidation of this coenzyme to take

place in the same compartment of the cell. This would then avoid the necessity of TPNH to unload electrons into the mitochondria, which may be a time-consuming process, especially in those tissues with a low mitochondria content. To pursue further the idea of the interaction between the dehydrogenases of the shunt mechanism and glutathione reductase, other tissues were assayed to see whether a correlation existed between the distribution of the enzymes concerned. Various tissues from rabbits were, therefore, assayed, and the results of the distribution of these enzymes is shown in Table 2. It would appear that there is no positive correlation, since the adrenal gland has the highest dehydrogenase activity but a low reductase activity. However, this tissue is unique, since TPNH is necessary for the enzymes in steroid formation.[21] In other tissues there appears to be a good correlation between the distribution of these enzymes, indicating that those tissues with high dehydrogenase activity also possess high reductase activity. Heart and skeletal muscles are both low in dehydrogenase and reductase activities. It seems that in other tissues there exists the possibility of interaction between these two enzyme systems. However, in lens the reductase may play a more important role than in other tissues because, with the exception of the epithelium, cytochrome activity has never been clearly demonstrated.

TABLE 2.—*Distribution of Enzymes in Various Tissues*

Tissue	Animal	Dehydrogenases, Units*/Gm.		GSH Reductase, Units/Gm.
		G-6-P	6-PG	
Liver	Bovine	60	72	405
	Rabbit	83	90	373
	Rat	45	65	270
Corneal Epithelium	Bovine	103	110	350
Adrenal	Rabbit	752	245	150
Kidney cortex	Rabbit	68	88	450
Kidney medulla	Rabbit	78	55	220
Spleen	Rabbit	25	53	140
Heart	Rabbit	15	8	34
Skeletal muscle	Rabbit	4	4	14

*A unit of enzyme is the amount which reduces or oxidizes 0.01 μM of TPN per minute. The assays are made after the reduction or oxidation of TPN spectrophotometrically, and the conditions employed have been previously reported. [6,19]

If one accepts the possibility that the GSH reductase can participate in such an oxidative mechanism, an interesting speculation can be made to explain the presence of glutathione in lens. In the glycolytic pathway, the oxidation of glyceraldehyde phosphate to diphosphoglyceric acid (Fig. 1)

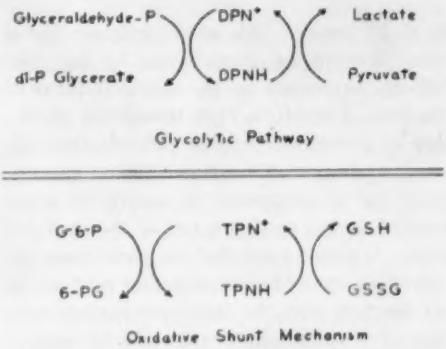


Fig. 1.—Coupled oxidation-reduction reactions.

results in the reduction of diphosphopyridine nucleotide (DPN). For glycolysis to continue it becomes essential to reoxidize the DPNH formed. The glycolytic scheme is fortunate in having available a "built-in" oxidation-reduction system, in which the DPNH is reoxidized by pyruvate and the latter is converted to lactate. A similar situation may be involved in the shunt mechanism; the oxidation of glucose-6-phosphate or 6-phosphogluconate brings about the reduction of TPN. The GSSG-GSH functions in a manner similar to the pyruvate-lactate system—namely, in the reoxidation of the reduced coenzyme. This comparison may be carried a step further; if lactate is found in the lens as the result of the glycolytic mechanism, then the presence of glutathione may be regarded as reflecting the result of the alternate oxidative pathway.

Can this mechanism alone explain the high glutathione content of the lens when the shunt mechanism plays a limited role in glucose metabolism? Perhaps the reoxidation of glutathione is so sluggish that a large amount of GSH is necessary to maintain a certain level of GSSG. Upon assaying for GSSG (Table 3) we found a greater amount of GSH after electrolytic reduction

TABLE 3.—*Glutathione and Oxidized Glutathione Content of Bovine Lens*

	Observations, No.	Glutathione, Mg./100Gm.±S.E.
Glutathione, reduced form	78	304.1±1.9
Glutathione, oxidized form	25	11.3±1.3

in all 25 lenses. This would indicate that a small amount of glutathione, 11 mg. per 100 cc., is present as the oxidized form in the lens. Therefore, even though the oxidation of glutathione may be difficult, the high concentration of 304 mg. per 100 cc. appears to be out of proportion to insure the presence of such a small amount of the oxidized form. It would seem that the glutathione involved in an oxidation-reduction reaction in conjunction with the shunt mechanism only partially explains its presence in the lens.

Section II. Peptidase Activity of Lens.—To obtain some measure of the stability of glutathione in the lens, the hydrolytic action of the lens on this tripeptide and other peptides was studied. Peptides were incubated in lens homogenates at 38 C, and the extent of their hydrolysis was measured either by the release of free glycine, by the increase in the ninhydrin reactive compounds, or, in the case of glutathione, by the amount of cysteinylglycine released.

The results shown in Table 4 indicate that although the hydrolytic action of lens homogenate effectively splits most peptides it seems peculiarly inactive against glutathione. An hour incubation with lens homogenate was sufficient to effect considerable hydrolysis of most peptides, but only a small fraction of glutathione was split even when it was incubated for three hours. It appears that the γ-glutamyl bond is the resistant site on the glutathione molecule, for lens homogenate is not capable of splitting γ-glutamylglycine. Apparently in the lens there is no enzyme which is able to attack the γ-glutamyl bond. However, the α-glutamyl bond is easily split by lens peptidases, as evidenced by the hydrolysis of α-glutamyl glutamate. The specificity of the lens peptidases is also demonstrated by the fact that the dipeptide, cysteinylglycine, is rapidly hydrolyzed but the cysteinylglycine bond in the glutathione molecule is not affected by lens homogenates.

TABLE 4.—*Peptidase Activity of Bovine Lens Homogenate* *

Peptide	Incubation Period, Hr.		% of Peptide Hydrolyzed
Glycylleucine	1		80–85
Leucylglycine	1		37–40
Glycyltyrosine	1		31–35
α-glutamyl glutamate	1		18–20
Cysteinylglycine	1		14–19
Glycylglycine	1		12–17
Leucylglycylglycine	1	(complete hydrolysis)	8–12
Glutathione	3	to cysteinylglycine	<2
(γ-glutamylcysteinylglycine)		to glycine	<2
γ-glutamylglycine	3		<2

*Ten micromoles of peptide were incubated with 7.5 mg. lens protein (dry weight) at 38 C in phosphate buffer, pH 7.4, and the total volume was 2.0 ml.

TABLE 5.—*Separation of Leucylglycine and Glycylleucine Dipeptidases*

	Activity*	
	Glycylleucine	Leucylglycine
Original lens homogenate	12.0	6.2
30%–40% fraction	7.8	1.6
40%–60% fraction	6.9	5.2
40%–60% fraction after treatment with calcium phosphate gel	6.5	0.2
Eluant of gel	0.1	14.5

*Activity is expressed as micromoles of peptide split in one hour by 10 mg. (dry) protein. It was measured by the amount of glycine released when 10 μM of peptide was incubated for 30 minutes at 38 C in 0.1 M phosphate buffer, pH7, in presence of the protein fractions. The protein concentration was adjusted so that less than 50% of the peptide was hydrolyzed.

Zeller et al.[22] have previously studied the peptidase activity of the lens. Their study suggests the possibility that, instead of one enzyme being responsible for the hydrolysis of all peptides, each peptide may be acted on by a distinct enzyme. Further evidence supporting this view was obtained by affecting a separation of the two most active lens dipeptidases. The procedure for the separation of the glycylleucine and leucylglycine dipeptidases is described in the section on Methods. The results, summarized in Table 5, show that the ammonium sulfate fractionation did not achieve a very good separation of the dipeptidases. The leucylglycine dipeptidase appears to be concentrated in the 40%-60% fraction, whereas the glycylleucine dipeptidase is about equally distributed between the two fractions. The

addition of the calcium phosphate gel to the 40%-60% fraction seemed to remove the leucylglycine peptidase but did not adsorb any of the glycylleucine peptidase. Therefore, the glycylleucine enzyme was recovered in the supernatant fluid after centrifugation. The leucylglycine peptidase was removed from the gel by extraction with 0.1 M Na_2HPO_4. The higher activity of the leucylglycine dipeptidase in the sodium phosphate eluant indicates that the enzyme had been concentrated and purified twofold over the initial homogenate. The lower glycylleucine peptidase activity of the various fractions than that observed in the original homogenate suggests that during the fractionation procedures either there occurred some denaturation of the enzyme or a necessary cofactor was lost. However, the addition of the supernatant fluid of a boiled lens homogenate or manganese or cobalt ions did not appreciably increase the peptidase activity of these fractions.

These studies on the lens peptidase activities demonstrate that one of the contributing factors for the accumulation of glutathione in lens is the relatively slow process by which glutathione is hydrolyzed.

Section III. The Extractability of Lens Glutathione.—Since glutathione is not rapidly destroyed in lens, the factor which may govern the amount of this peptide is its diffusion out of lens. To study this aspect of glutathione metabolism, its extractability was followed by incubating lens in a hypertonic phosphate solution for varying periods up to four hours. The amount of glutathione retained in the lens and that released into the medium was determined. The results are shown in Figure 2. The glutathione value normally found in lens was determined on 78 lenses. Each point representing the period of incubation was determined by at least eight lenses. The spread of the values obtained is noted on the graph. Initially there appears to be a fairly rapid extraction of lens glutathione, but very little is extracted between the second and fourth hours of incubation. The amount found in the medium represents total glutathione, GSH and GSSG, which diffused from lens and is expressed in terms of the lens weight. Only the reduced glutathione of lens is recorded on this graph, but the amount of GSSG would contribute very little to the values. The sum of the glutathione found in the lens and medium does not change significantly during the incubation.

At first, it was thought that the extractability curve reflected an equilibrium state, one in which approximately 80% of the glutathione was retained in lens and 20% found in the media. If this were the case, a continual drop in lens GSH would be observed if fresh buffer were substituted at the end of each hour. However, when this experimental procedure was carried out no further drop in GSH content was observed. These results were confirmed by another experiment, one in which an active glutathione-splitting enzyme, purified from bovine kidney,[23] was placed in the medium in which lens was incubated. Under these circumstances, as glutathione diffused out of lens it would be rapidly split and if an equilibrium were involved a progressive drop in glutathione content should be observed. However, four hours of incubation in the presence of this enzyme lowered the GSH content of lens by no more than 23% of the original value. The extractability of GSH was not affected whether the incubating medium was at pH 5.5, 7.4, or 8.0 or whether the gas phase was air or nitrogen. The concentration of the extraction medium had some effect on the extractability. In isotonic phosphate buffer or in Krebs-Ringer buffer, as shown in Figure 3, GSH was only slowly extractable. On the other hand, hypotonic and hypertonic phosphate solution have a similar extractability curve. The greatest effect was observed when lens was incubated in hypertonic phosphate buffer which contained either 3.0 M urea or 1.5 M guanidine hydrochloride. In these cases, lens GSH was rapidly extracted. The glutathione extracted could be recovered in the medium. When the experiment was run under nitrogen to prevent the oxidation of glutathione

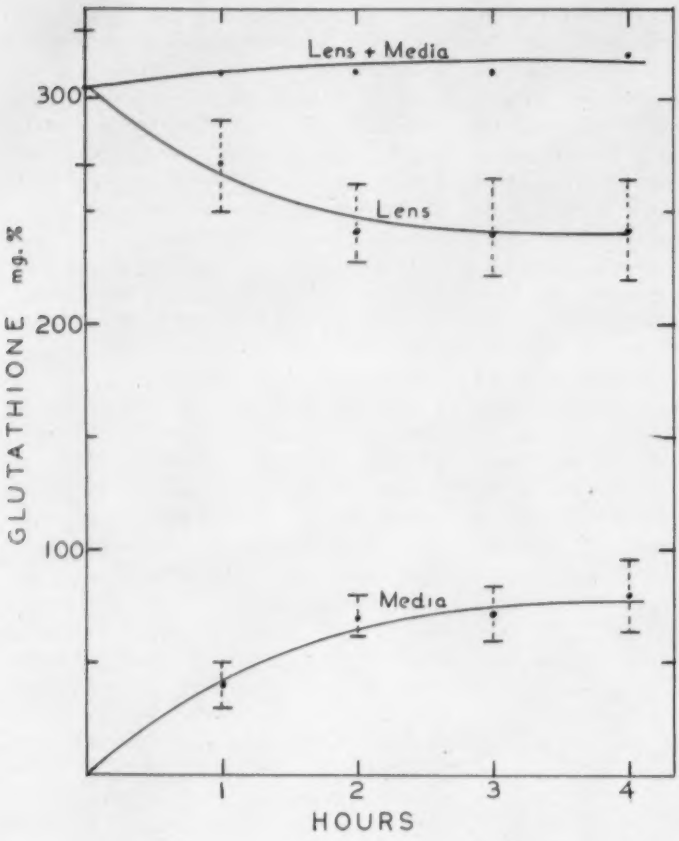


Fig. 2.—Extractability of lens glutathione.

in the media, the sum of the GSH in the lens and medium was equal to the value normally found in lens. In these cases, the effect is not due to the extreme hypertonicity of the solutions, for 3.0 M glucose or 3.0 M NaCl had no such effect. Apparently, urea and guanidine, known for their ability to split hydrogen bonds, caused the rapid extraction of glutathione by releasing it from the binding sites.

These extraction studies suggest that of the glutathione found in lens approximately 20% may be considered as "free" glutathione. In situ, since it is difficult to demonstrate the presence of GSH or GSSG in the aqueous humor, even this fraction is not readily diffusible. This is indicated by the slow diffusion of GSH from lens in isotonic solutions. The small amount observed in the isotonic medium may be due to the mechanical agitation incurred by the lens during the incubation procedure. When the lens is incubated in the hypo- or hypertonic medium this fraction is made readily extractable, either because these solutions affect the permeability of the lens or perhaps because they release GSH from weak binding sites.

The major fraction of glutathione appears to be bound in some manner. Since concentrated urea and guanidine solutions caused a rapid extraction of lens glutathione, and similar strengths of glucose or sodium chloride had no effect, it seems that some type of hydrogen bonding is involved. Just what purpose this fraction of glutathione serves in lens and just what relationship it has with the protein sulfhydryl groups are questions still to be investigated.

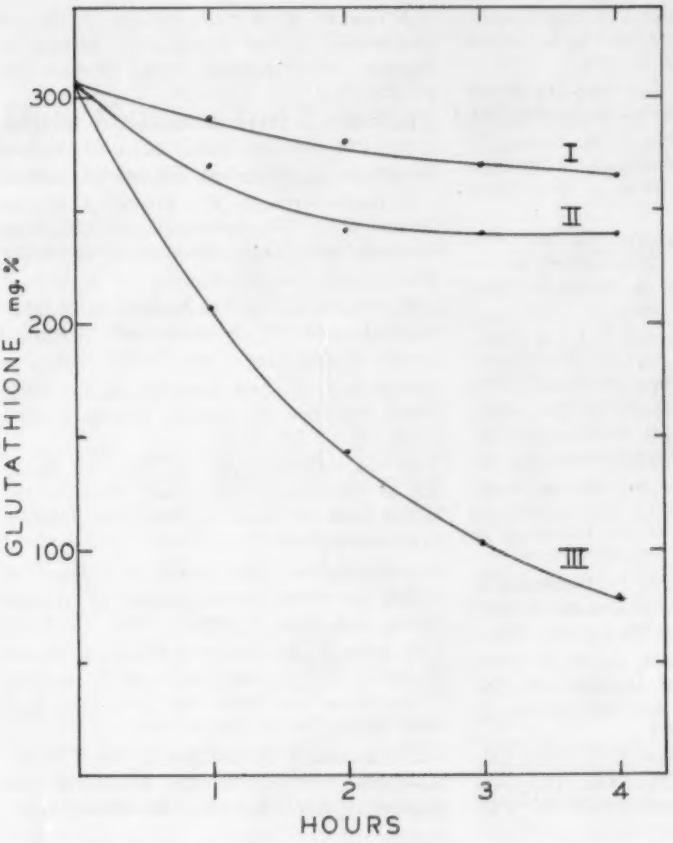


Fig. 3.—Influence of various media on extractability of lens glutathione. *I*, isotonic phosphate buffer and Krebs-Ringer buffer; *II*, hypotonic or hypertonic phosphate buffer; *III*, 3.0 M urea or 1.5 M guanidine hydrochloride in hypertonic phosphate buffer.

Summary

Various factors influencing the state of glutathione in the lens have been studied. The manner in which glutathione may participate in carbohydrate metabolism is discussed. It appears possible that an interaction of the dehydrogenases of the shunt mechanism and glutathione reductase may exist.

Although the lens possesses a high peptidase activity, it does not have the ability to hydrolyze glutathione very rapidly. Apparently, there is no active enzyme which is able to split the γ-glutamyl linkage of glutathione.

Extractability studies of lens glutathione have suggested that approximately 20% is readily extractable. Since concentrated urea and guanidine solutions can effect a rapid extraction of lens glutathione, it appears that a major fraction of glutathione is bound to lens protein by hydrogen bonding.

243 Charles St. (14).

REFERENCES

1. Pirie, A., and van Heyningen, R.: Biochemistry of the Eye, New York, Oxford University Press, 1956, pp. 19-22 and 60-63.

2. Kinsey, V. E., and Merriam, F. C.: Studies on the Crystalline Lens: II. Synthesis of Glutathione in the Normal and Cataractous Lens, Arch. Ophth. 44:370-380, 1950.

3. Daisley, K. W.: Synthesis of Glutathione by Normal and X-Irradiated Lens, Biochem. J. 60:xl, 1955.

4. Kinoshita, J. H., and Masurat, T.: The Direct Oxidative Carbohydrate Cycle of Bovine Corneal Epithelium, Arch. Biochem. 53:9-19, 1954.

5. Kinoshita, J. H.; Masurat, T., and Helfant, M.: Pathways of Glucose Metabolism in Corneal Epithelium, Science 122:72-73, 1955.

6. Kinoshita, J. H.: Carbohydrate Metabolism of Lens, A. M. A. Arch. Ophth. 54:360-368, 1955.

7. Ashmore, J.; Kinoshita, J. H.; Nesbett, F. B., and Hastings, A. B.: Studies on Carbohydrate Metabolism in Rat Liver Slices, J. Biol. Chem. 220:619-626, 1956.

8. Alexander, B.; Landwehr, G., and Seliman, A. M.: A Specific Micromethod for the Colorimetric Determination of Glycine in Blood and Urine, J. Biol. Chem. 160:51-59, 1945.

9. Schwarz, T. E., and Engle, F. L.: A Photometric Ninhydrin Method for the Measurement of Proteolysis, J. Biol. Chem. 184:197-202, 1950.

10. Binkley, F., and Nakamura, K.: Metabolism of Glutathione: I. Hydrolysis by Tissues of the Rat, J. Biol. Chem. 173:411-421, 1948.

11. Binkley, F.; Fujii, S., and Kimmel, J. R.: Metabolism of Glutathione: II. Determination of Glutathione and Products of Its Hydrolysis in Blood, J. Biol. Chem. 186:159-162, 1950.

12. Olson, C. K., and Binkley, F.: Metabolism of Glutathione: III. Enzymatic Hydrolysis of Cysteinylglycine, J. Biol. Chem. 186:731-735, 1950.

13. King, F. E., and Kidd, P. A. A.: New Synthesis of Glutamine and Dipeptides of Glutamic Acid from Phthalylated Intermediates, J. Chem. Soc. 4:3315-3319, 1949.

14. Strittmatter, P., and Ball, E. G.: Formaldehyde Dehydrogenase, a Glutathione Dependent Enzyme System, J. Biol. Chem. 213:445-461, 1955.

15. Grunert, R. R., and Phillips, P. H.: A Modification of the Nitroprusside Method of Analysis for Glutathione, Arch. Biochem. 30: 217-225, 1951.

16. Dohan, J. S., and Woodward, G. E.: Electrolyte Reduction and Determination of Oxidized Glutathione, J. Biol. Chem. 129:393-403, 1939.

17. Bhattacharya, S. K.; Robson, J. S., and Stewart, C. P.: The Determination of Glutathione in Blood and Tissues, Biochem. J. 60:696-702, 1955.

18. Gregory, J. D.: The Stability of N-Ethylmaleimide and Its Reaction with Sulfhydryl Groups. J. Am. Chem. Soc. 77:3922, 1955.

19. Rall, T. W., and Lehninger, A. L.: Glutathione Reductase of Animal Tissues, J. Biol. Chem. 194:119-130, 1952.

20. Van Heyningen, R., and Pirie, A.: Reduction of Glutathione Coupled with Oxidative Decarboxylation of Malate in Cattle Lens, Biochem. J. 53:436-444, 1953.

21. Haynes, R., and Berthel, L.: Effect of ACTH on Corticosteroid Content of Adrenal Tissue, Fed. Proc. 15:270-271, 1956.

22. Zeller, E. A.; Daily, L.; Wakim, K. G., and Herrick, J. F.: Contributions to the Enzymology of the Normal and Cataractous Lens, Proc. Staff Meet. Mayo Clin. 26:194-199, 1951.

23. Kinoshita, J. H., and Ball, E. G.: A Transpeptidation Reaction Between Glutathione and Arginine, J. Biol. Chem. Soc. 200:609-617, 1953.

Data Camera for Labeling Ophthalmic Stereograms

HERMAN J. NORTON Jr., M.D., Rochester, N. Y.

In a previous publication [1] concerned with a system of panophthalmic stereophotography, brief mention was made relevant to a unit of the system used for permanently labeling ophthalmic stereotransparencies. The present communication presents the details of this photographic instrument.

Generally speaking, when a photograph is made there are usually important data pertinent to the picture. The high value of such data is manifest when one is dealing with scientific photography, and it increases still further in importance when the field is medicine, where pathological recordings may have significant direct bearing on the diagnosis, prognosis, and therapy of human afflictions.

There has long been a need for the elimination of the usual data record book or sheets, which are not infrequently mislaid, mixed up, or lost completely after photography. In addition, eradication of the inevitable time-consuming label period once transparencies are returned from the laboratory is desirable. Thirdly, it is evident that a photographically labeled picture has to be permanently marked at the time of the original exposure. It is reasonable to believe that such a photographic record is increased considerably in forensic value over the one labeled by hand several days after exposure either from memory or from ill-kept records.

Received for publication Sept. 6, 1956.

From the Department of Surgery, Division of Ophthalmology, of the University of Rochester Medical Center.

Aided in part by a grant from the Ophthalmological Foundation, Inc., New York, and the Department of Research, New York Association for the Blind.

The Stereofilm Format

In the attempt to develop a maximally composite and efficient system of ocular stereography, a 35 mm. film pack was adopted. Such a choice, as described in the above-mentioned publication, has many advantages, one being that it permits the surgeon-filmer to label each individual stereogram permanently at the time the exposure is actually made.

The color film strip used measures 100×35 mm. Corresponding points in each component of the stereoscopic pair are 63 mm. apart, and the distance between the inner edges of each picture is about 45 mm. It is the existence of the 45 mm. interpicture space which makes individual permanent labeling possible, whereas had 35 mm. roll-type film been chosen such a data system would be impossible. The dimensions of the exposed interpicture data area are 24×22 mm. This represents a considerable minification of the original camera data card, measuring 60×48 mm. It has been found that this is ample room for data relevant to a particular stereogram. Information including the patient's name, age, hospital number, and date as well as the eye involved, diagnosis, treatment, and disposition fits conveniently in the interpicture space provided. All data are easily read by holding the stereotransparency up to a light. We have found that permanent photographic labeling at the time of exposure has given rise to great satisfaction by increasing the accuracy of the recorded data through the elimination of errors which formerly crept in during the transfer of facts from a data book to the developed transparency. Figure 1 gives an over-all view of the 35 mm. film pack and a mounted simultaneously exposed retinal

Fig. 1.—A 35 mm. film pack with protective film slide partially pulled out and a mounted retinal stereotransparency.

stereogram, the later having been reproduced specifically to demonstrate the relationship of the data area to the components of the stereoscopic picture and not particularly to bring out the details of the retinal picture. Examination of the stereogram will reveal that the actual data area covers an area of 5.5 sq. cm. This means that an 8 to 10 mm. unexposed area remains between the data area and each component of the stereogram, thus preventing confluence of the two, which would obviously be an intolerable situation. Figure 2 shows an enlargement of the same stereogram with particular attention given to the retinal picture per se. It shows a normal fundus stereoscopically photographed.

Figure 3 shows the data card used in the photographic labeling system under discussion. The actual data area of the card covers about 28 sq. cm. This original area is then reduced by the optical system to 5.5 sq. cm. so that it will fit conveniently in the available interpicture space on the film. As shown, the physician's name and address can be printed on the top of each data card. This assures absolutely correct identification of all films, thus preventing loss or mix-up due to failure to include a name and return address. The small rectangular cut-out seen on the card helps to stabilize the card when it is in position in the camera. The information on the card is conveyed to the stereo film through the use of the data camera now to be considered.

The Data Camera

The camera is box-shaped, having a hinged cover which snaps shut over its superior surface. A square opening located in this surface overlies the camera lens below and coincides with the interpicture film space above. The film track of the superior surface of the data camera has the same dimensions as the track of the

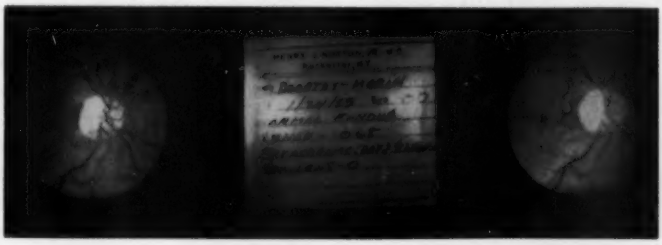


Fig. 2.—Magnification of the labeled retinal stereogram, showing details of the fundus picture and data area.

CHARLES T. SULLIVAN, M. D.
HERMAN J. NORTON, JR., M. D.
797 ELMWOOD AVE., ROCHESTER 23, NEW YORK

JOHN SMITH, 26 YRS., 6/1/56
Px, VOD $\bar{e}$ +1.00 +.50 X 90 = 20/50
SLIGHT DISC-ELEVATION

DX, OPTIC NEURITIS

RX, A.C.T.H, VITAMIN B

Fig. 3.—A typical data card filled in, showing the physician's identifying letterhead above.

retinal stereocamera described in a past communication and therefore will accommodate the same 35 mm. film pack used in absolute retinal stereography. A metal band over the distal end of the film track, under which the film pack fits, holds the end of the pack in proper position when the camera is loaded, thus preventing the possibility of straining or springing the camera cover as it is closed. The last feature of the superior surface is a microswitch located at the center of the distal end of the film track. This will be considered in further detail under a description of the technique involved.

Four short rubber legs comprise the only characteristic of the inferior surface of the camera. These merely raise the base of the unit slightly and prevent it from sliding on smooth surfaces when the shutter is triggered at the time of exposure. The plunger actually makes contact with the shutter pin inside the camera.

One end of the camera contains the electrical supply cord, which enters to the inside, while the opposite end contains the data card already considered above. Most of the features described in the text can be seen in Figure 4.

The internal contents of the camera are divided into two parts: (1) the illuminating system and (2) the optical system. Light for the exposure is supplied by two small Christmas-tree-type lamps rated at 7 watts, 115-125 volts and operated off the conventional 60 cps wall current. These are located, one above the other, on the inside of the front surface of the camera, one at its upper and one at its lower edge. When the film pack is inserted into the camera and the camera cover is closed, the microswitch activates the lamps. With this illumination an exposure of 0.04 second at $F/4$ has been found to be proper. When such lamps are used, no built-in transformers are required, promoting lightness of weight as well as maximum efficiency and compactness. The optical system through which the data card facts are conveyed to the interpicture space on the stereogram is composed of the following elements: (1) the data card or object contained in the slot at the end of the camera, (2) a 45-degree plane mirror positioned at the midpoint of the interior of the camera housing, (3) an Ilex 3.5 lens attached to the undersurface of the top of the camera and in line with the square opening described above. The camera lens positioned above the mirror conveys the data card image formed in the mirror so that

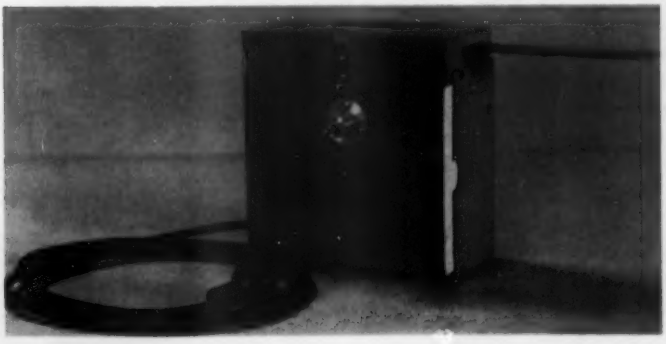


Fig. 4.—The data camera, showing plunger trigger, data card in position at end of camera, and protective film slide pulled out ready for exposure.

it comes to focus on the film contained in the film pack above.

Use and Technique

The aim has been to so simplify the labeling process that little learning is required to obtain absolute accuracy. In this way, once the physician has made the stereo-ophthalmic exposure and has filled in the data card he may turn the task of photographic labeling over to his secretary with the assurance that the data he has written down on the card will be exactly reproduced on the stereogram.

To make the technique clear, we may assume that the physician has just completed taking a stereotransparency photograph of the retina. Since there are important data in the case, he now wishes to make a permanent record of the facts on the individual stereogram. The next step is merely to fill out a data card, as shown in Figure 3. The completed card and stereo pack are then handed to the secretary, who keeps the labeling camera on her desk. She inserts the card into the card slot at the end of the camera, places the film pack in the track on the superior surface of the camera, and closes the camera cover. At this point the lamps are on. Next, the film slide is pulled out and the trigger plunger is pushed. This is shown in Figure 4. The protective film slide is then pushed in and the film pack is removed, all data having been permanently photographed on the particular stereogram involved. The stereophoto is then ready for immediate processing. There are perhaps only two ways an error can be made. They are (1) that the protective slide may not be pulled out before the camera plunger is pushed and (2) that the film pack may accidently be removed from the camera before the protective slide is pushed back in. In the case of the former no data will appear on the processed stereogram, for no exposure is made. In the latter case, of course, the entire film will be spoiled through exposure to daylight.

The only part the physician plays in the data-labeling process is to record his remarks on the data card, after which the entire procedure is handled by the secretary, thus relieving the physician for other important duties. The achievement has thus been to minimize the time devoted to "on the spot" labeling by the physician while obtaining a high degree of permanent accurate film marking. Since the shutter speed and the diaphragm aperture are set at a fixed point, as already mentioned, no such adjustments are required by the secretary at the time of exposure.

Summary

The second unit of a system of ocular stereophotography is presented. A compact camera for permanent photographic labeling of individual ophthalmic stereograms is considered. The unit is a 35 mm. film pack camera. The camera makes it possible to utilize the interpicture space between the two components of ophthalmic stereograms, either intraocular or extraocular. Data pertinent to the stereogram are recorded in the interpicture space by the labeling camera.

The form of the camera, including the optical and illuminating systems, is described. An account of the suggested technique is given.

Mr. A. S. Clarke, of Washington, D. C., gave help during the development of the unit.

1135 S. Winton Rd. (18).

REFERENCE

1. Norton, H. J., Jr.: Absolute Electronic Retinal Stereophotography, Am. J. Ophth. 40: 809-917, 1955.

Metastasis of Adenocarcinoma of Colon to Conjunctival Surface of Lid

PAUL J. OSTRIKER, M.D., Stamford, Conn.

Although many varieties of primary neoplasms may involve the eyelids, it is most unusual for the lids to be the site of a distant metastasis of a malignant tumor. This is a case report of an adenocarcinoma of the colon with a distant metastasis presenting on the conjunctival surface of the lid. No previous report of a primary neoplasm with distant metastasis to this site could be found in the literature, and only one other case has been reported[1] wherein a neoplasm had a distant metastasis to the eyelid at all.

Report of a Case

The patient, a 57-year-old white man, first came to the attention of his general surgeon, Dr. Sidney M. Cohen, of Jackson Heights, N. Y., in October, 1953, complaining of bowel irregularity and bloody stools for several weeks. A palpable mass was present in the right lower abdomen, and x-rays were highly suggestive of a neoplasm of the lower ascending colon. A right hemicolectomy and ileotransverse colostomy were performed. No spread of the tumor to the liver or regional lymph nodes was seen grossly. Microscopic studies of the specimen revealed it to be an adenocarcinoma of the colon, Grade 2, with no extension to the regional nodes.

The patient had an uneventful postoperative course, remaining well until December, 1954, at which time he developed vague abdominal pains and began to lose weight. X-rays did not reveal any lesion intrinsic to the gastrointestinal tract, but the weight loss continued and a nodular enlargement of the liver was noted after a few weeks. His course went steadily downhill, and jaundice developed.

Received for publication July 10, 1956.

In May, 1955, one and one-half years after his abdominal surgery, the patient began to complain of an irritation of his right eye. A growth was seen projecting from the right upper lid and rubbing against the globe. The lid lesion grew rapidly, and, although he was a terminal carcinoma patient, the eye irritation seemed to be one of his sources of greatest discomfort. An ophthalmologic consultation was requested three weeks after the first appearance of the lid tumor.

On examination the patient was found to have a pedunculated cylindrical tumor projecting from the conjunctival surface of the right upper lid and about 4 mm. in length. It arose from a rather broad base 2 mm. superior to the middle of the upper lid margin, and its distal end extended about 2 mm. below the lid margin. The lesion produced extensive abrasions of the superior one-third of the right cornea. The surface of the growth was somewhat irregular, and there was some serosanguinous discharge from the ulcerated distal end.

The lesion was excised, with use of local anesthesia, and was found to be very friable during the procedure. The dissection had to be carried into tarsal tissue to remove the gross lesion in toto. There was no clinical reappearance of the lid tumor at the time the patient died, three weeks later. The specimen was sent to Dr. David Grayzel, pathologist, Jewish Hospital of Brooklyn, for microscopic study. His report follows.

Microscopic Study.—The section consists almost entirely of tumor. This tumor is a well-differentiated adenocarcinoma composed of small and large glandular structures lined by tall columnar cells varying in size, shape, and nuclear staining. The latter

are large, irregular, and hyperchromatic. Mitotic figures are seen in moderate numbers. The cells are heaped up and show loss of cell polarity. Some of the tumor cells appear to be mucin-secreting, and within some dilated lumina there is a faintly basophilic-staining mucinous material. The histologic picture is typical of adenocarcinoma of the intestinal tract.

Diagnosis: Metastatic well-differentiated adenocarcinoma.

Photomicrograph showing metastatic adenocarcinoma of the conjunctival surface of the lid with histologic picture typical of adenocarcinoma of the intestinal tract.

Comment

A survey of the literature fails to reveal any other case of a distant metastasis of a neoplasm to the conjunctival surface of the lid. The only other reported case, to my knowledge, of a neoplasm that had distant metastasis to the eyelid at all is that of Thomas Cowan.[1] In his case an adenocarcinoma of the stomach metastasized to the eyelid, presenting on the skin surface of the lid and mimicking a chalazion. Vrabec reported a case[2] of a tumor of the upper lid secondary to an ipsilateral parotid gland tumor which proved to be invasive by direct lymphatic spread. This represents spread by direct extension rather than a distant blood-borne metastasis. There is no mention of metastatic tumors of the eyelid in Reese's[3] monograph, "Tumors of the Eye," or in the section on tumors of the eyelid in the fifth volume of Duke-Elder's[4] "Textbook of Opthalmology" or in R. A. Willis' textbook, "The Spread of Tumors in the Human Body."[5] Generalized lymphomas that involve the eyelids along with other sites in the body are generally regarded as being neoplasms of multicentric foci rather than metastasizing to the distant sites.

Gastrointestinal tumors rarely do metastasize to the head and neck, most of them being arrested in the liver.[5] In one series[5] of 179 cases of tumors arising in the portal area, 86 cases (48%) had hepatic metastases, whereas only 35 (19%) of these had pulmonary metastases. Most intestinal tumors that metastasize to the lungs do so by first metastasizing to the liver and invading the efferent hepatic veins. However, intestinal neoplasms may also spread to the lungs via the thoracic duct.

Those blood-borne tumor emboli that do get beyond the liver and into the lungs are usually arrested in the lung capillaries. However, if there were not merely transport of the tumor embolus to the lung but an actual secondary growth which infiltrated and entered a pulmonary vein, it can be seen how such a tumor embolus could pass to the left side of the heart and then to the head and neck. In this case there was no clinical evidence of pulmonary metastasis, but since an autopsy was not performed this cannot be excluded.

In those cases where secondary infiltrative growths in the lungs can be excluded the method of transport of these paradoxical tumor emboli from the gastrointestinal tract or, for example, from the prostate to the head and neck region has been a subject of interesting speculation. The presence of a

patent foramen ovale or interventricular septal defect must provide only a rare explanation for bypassing of the lungs in these cases. Uninterrupted transpulmonary passage of solitary tumor cells has been postulated, but tumor emboli almost always consist of groups of cells and are appreciable fragments of growth which are too large to pass through the pulmonary capillaries. Batson [6] described a system of vertebral veins with reversible directions of blood flow that traverse the length of the spinal column and anastomose with the abdominal, thoracic, cervical, and cranial veins. The above-mentioned tumors might thus bypass the heart and lungs and metastasize to the head and neck through these veins. Willis [5] does not believe it is usually necessary to explain the spread of intestinal tumors to the peripheral organs by such unusual mechanisms as the vertebral veins or foramen ovale or transpulmonary passage of solitary tumor cells. He believes, citing his own experiences, that in these cases when a really painstaking histopathologic study of serial sections of both lungs is performed a malignant embolus or small metastasis in the lung can almost always be demonstrated. Any further discussion of this question is beyond the scope of this report.

Summary

A report is presented of a patient with adenocarcinoma of the colon with metastasis to the conjunctival surface of the eyelid one and one-half years after abdominal surgery. Microscopic study of the excised lid tumor showed it to be a well-differentiated adenocarcinoma conforming to the primary neoplasm in the colon. This is believed to be the first reported case of a distant metastasis of a neoplasm to the conjunctival surface of the lid and the second reported case of a distant metastasis of a neoplasm to any part of the eyelid. Possible mechanisms of spread of the colonic tumor to the eyelid are briefly considered.

480 Bedford St.

REFERENCES

1. Cowan, T. W.: Adenocarcinoma of the Lid, Secondary to Adenocarcinoma of the Stomach, A. M. A. Arch. Ophth. 48:496-497 (Oct.) 1952.

2. Vrabec, F.: Contributions to the Study of Metastatic Tumors of the Eyelids, Ophthalmologica 122:362-366 (Dec.) 1951.

3. Reese, A. B.: Tumors of the Eye, New York, Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers), 1951.

4. Duke-Elder, W. S.: Textbook of Ophthalmology, St. Louis, The C. V. Mosby Company, 1952, Vol. 5.

5. Willis, R. A.: The Spread of Tumors in the Human Body, London, Butterworth & Co. Ltd., 1952.

6. Batson, O. V.: The Role of the Vertebral Veins in Metastatic Processes, Ann. Int. Med. 16:38-41 (Jan.) 1942.

Case Reports

Tabetic Optic Atrophy

Fifteen-Year Follow-Up After Treatment Without Progression

ERNEST D. HELMICK, M.D., Philadelphia

Tabetic optic atrophy in the past has been notoriously resistant to treatment. In an occasional case spontaneous arrest has occurred and the atrophic process has remained stationary without antisyphilitic treatment. In most cases the degenerative process manifests itself by a typical visual field defect in one eye and then involvement of the second eye occurs sooner or later unless checked by treatment.[1,2] The following case is of interest because of the absence of change in the visual status of a patient with tabetic optic atrophy observed over a 15-year period and because of the low total dose of penicillin which apparently arrested the syphilitic process.

Report of Case

A 49-year-old white male clerk was first seen in the Syphilology Clinic of the Hospital of the University of Pennsylvania on Dec. 8, 1941, upon referral of his local physician because of a positive serologic test for syphilis. Consultation with the ophthalmology service revealed that the vision in the patient's left eye had been failing for the previous eight months. Records from his private oculist showed that on Jan. 18, 1939, he had full visual fields and 6/6 vision in each eye, with normal fundi. On Nov. 12, 1941, vision in the right eye was recorded as 6/6, while visual acuity of the left eye had decreased to counting fingers at 4 meters, with a large temporal field defect involving fixation. The past history was also significant in that the patient had a penile lesion diagnosed clinically as a chancre in 1931. His blood Wassermann reaction shortly thereafter was found to be positive, and he received 30 intramuscular heavy metal injections and was discharged as cured. He continued asymptomatic until the early part of 1941, when he first noticed decreased vision in his left eye.

On initial examination in the eye clinic, on Dec. 14, 1941, vision was recorded as 6/6 for the right eye and hand movement for the left eye. The pupils reacted briskly but through a limited arc to light directly and consensually. There was no irregularity of the pupils, and the reaction to convergence was equal to that of light. The pupils were normally positioned and dilated in the dark. Marked pallor of the disc was present on the right. The left disc was very pale and gray and showed definite primary optic atrophy, well advanced. The perimetric visual field of the right eye showed minimal contraction, while the left eye had only a superior nasal island of vision to the same 1 mm. white test light. The central field for the right eye was normal, and in the left eye there remained only an irregular superior nasal island to the 20/1000 white isopter (Fig. 1).

Significant findings on neurologic examination were an absence of the cremasteric, knee, and ankle reflexes. Position sense was good, and mental processes were considered normal. The Kolmer, Eagle, and Kline serological tests were positive. The cerebrospinal fluid contained 52 cells per cubic millimeter, with a 4+ Wassermann and a tabetic colloidal gold curve (3444210000). On Dec. 15, 1941, he was again started on

Received for publication July 3, 1956.

From the Department of Ophthalmology, Hospital of the University of Pennsylvania.

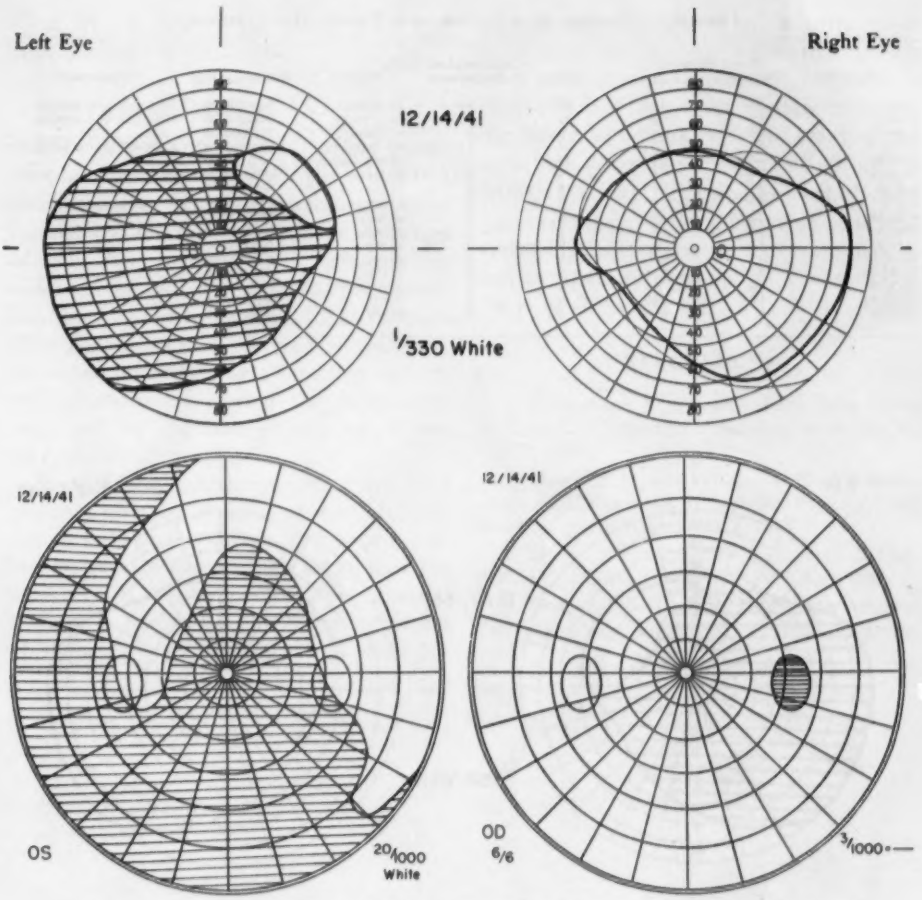


Fig. 1.—Peripheral and central visual fields during the active stage of tabetic optic atrophy.

systemic heavy metal therapy (bismuth and arsenic) and was given 18 Swift-Ellis treatments. He continued on this until Jan. 20, 1943, when his blood serology and cerebrospinal fluid were negative. In December, 1943, ocular and neurologic examination remained unchanged, but his blood serology and cerebrospinal fluid again showed evidence of syphilitic activity. He was then given penicillin therapy of 1,200,000 units, with the subsequent conversion to normal of the cerebrospinal fluid (Table).

The patient's neurologic status remained unchanged in the intervening years. The ocular findings on periodic reexaminations remained the same. On Dec. 7, 1955, vision in the right eye was 6/6 and in the left eye was hand movement. The pupils were slightly irregular but equal in size. The pupillary response to light was somewhat sluggish, with contraction through a small arc, but the near reaction was prompt. Ocular tension was 16 mm. Hg Schiøtz in each eye. The right fundus showed a pale disc with sharp outline and with some fine perivascular pigment deposition in the midperiphery. The left disc showed advanced atrophy, with marked pallor, a sharp margin, and visible lamina cribrosa. The retinal arterioles were moderately attenuated. Peripheral and central visual fields were essentially unchanged from those taken in 1941

Laboratory Findings in a Patient with Tabetic Optic Atrophy

Date	Blood Serology Kolmer	Kline	Cerebrospinal Fluid Cells	Wasserman	Protein	Colloidal Gold	Treatment
12/8/41	4+	+	52	4+	4+ Pandy	3444210000	Bismuth and arsenic
3/19/42	4+	+	12	2+	3+ Pandy	4442210000	Bismuth and arsenic
1/20/43	3+	−	2	0	− Pandy	1110000000	.....
12/14/43	4+	+	74	4+	4+ Pandy	3444210000	1,200,000 units penicillin
6/14/44	1+	1+	10	±	20 mg./100cc.	1111110000	.....
11/14/45	2+	+	0	0	30 mg.	0000000000	.....
6/7/46	2+	+	3	0	30 mg.	0000000000	.....
9/3/47	2+	+	2	0	30 mg.	0000000000	.....
9/22/48	2+	+	2	0	20 mg.	0000000000	.....
9/28/49	2+	+	2	0	20 mg.	0000000000	.....
11/1/50	1+	+	0	0	20 mg.	0000000000	.....
11/14/51	0	0	2	0	20 mg.	0000000000	.....
11/26/52	0	0	1	0	20 mg.	0000000000	.....
12/2/53	±	±	2	0	20 mg.	0000000000	.....
12/15/54	1+	1+	2	0	20 mg.	0000000000	.....
12/8/55	0	0	2	0	20 mg.	0000000000	.....

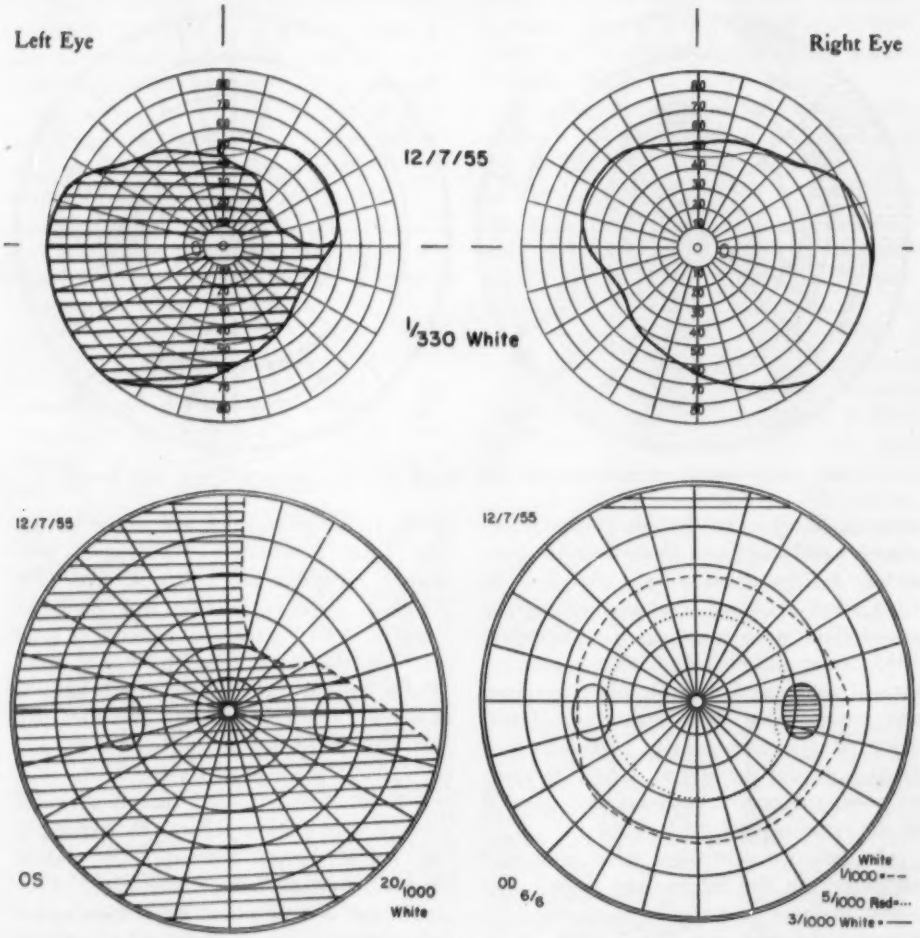


Fig. 2.—Peripheral and central visual fields after arrest of tabetic optic atrophy.

(Fig. 2). X-rays of the skull, orbit, and optic foramen were normal.

Comment

The patient developed tabetic optic atrophy approximately 10 years after a penile chancre. His response to heavy metal therapy was minimal. With the introduction of penicillin as an effective antisyphilitic agent in the summer of 1943, the patient was shortly afterwards given 1,200,000 units of penicillin. In spite of this low total dose, his visual and neurologic condition has remained stationary during the intervening years and the syphilitic process has shown no evidence of reactivation.

There is no correlation of spinal fluid response with the progress of optic atrophy. Spinal fluid abnormalities may improve or become normal even though atrophy of the optic nerves is progressing. Heavy metal therapy is known to slow the progression of syphilitic optic atrophy, but it does not prevent ultimate blindness. Malaria treatment improved the outlook somewhat, but most authors now agree that penicillin is more effective than fever therapy in arresting tabetic optic atrophy. For maximal results high doses of penicillin (10,000,000 to 20,000,000 units) are recommended.[3,4] Adequate treatment in the early stage of neurosyphilis is necessary to prevent optic atrophy and to assure preservation of vision.

1059 South 53d St. (43).

REFERENCES

1. Igersheimer, J.: Atrophy of the Optic Nerve in Tabes and Dementia Paralytica, Arch. Ophth. 42:170, 1949.

2. Moore, J. E., and Woods, A. C.: The Pathology and Pathogenesis of Syphilitic Primary Optic Atrophy, Am. J. Ophth. 23:1, 1940.

3. Moore, J. E.: Penicillin in Syphilis, Springfield, Ill., Charles C Thomas, Publisher, 1946.

4. Bruetsch, W. L.: Syphilitic Optic Atrophy, Springfield, Ill., Charles C Thomas, Publisher, 1953.

Clinical Notes, New Instruments and Techniques

Ophthalmologic Use of New Stereo Attachment

THEODORE N. ZEKMAN, M.D., Chicago

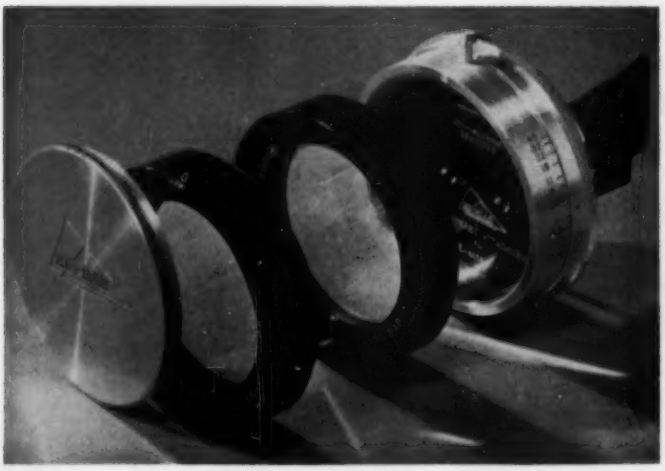
A lens for three-dimensional closeups, especially suitable for medical visualization, has been introduced as an attachment to the Exakta Model V or VX 35 mm. camera, having the outside bayonet type of flange onto which the attachment may be fitted. On older models the flange may be replaced at any qualified service shop to accommodate the attachment. Other adjustments can be made as required, according to accompanying instructions.

The device is called the Kin-Dar hypostereo attachment,* "hypo" because the lenses are set at less than normal interocular separation. It is designed for taking stereo pictures at distances of approximately 9 in. and closer. Photographs down to 3 in. from the subject are possible, with a surprising amount of depth even with small aperture shots, although it is best to have backgrounds and foregrounds fairly close to the main subject. The attachment has been planned for precision at fixed distances, so that focusing manipulation is not necessary. The working distance is varied by the use of achromatic supplementary lenses. For extreme close-up photographs, down to about 3 in. or somewhat less, a large supplementary lens is used in front of the objective lens.

Both pictures of the stereo pair are taken upon each conventional eight-perforation film space, so that the same number of stereo slides will be obtained from a roll of film as of 2×2 slides. In other words, the attachment produces two matching transparencies, each four perforations wide, which are then mounted for viewing in regular stereo viewers or may be used for projection. Stereo and 2×2 slides may be intermixed. The regular 35 mm. color or black and white film is used.

Received for publication Sept. 10, 1956.

* Kin-Dar Corporation, South Milwaukee, Wis.; distributed by Speedlight Center, 128 West 32d St., New York.



Stereo attachment for use with Exakta 35 mm. camera. Professional stereo close-ups down to 3 in. from subject are possible.

The field size desired is decided on and the proper lens combination attached according to a chart of field sizes and working distances. The camera, hand-held, is moved into proper position of framing and focus and tripped. A celluloid ground glass mask comes with the device to mask off one of the two images. The mask has a center cross to help center and frame the subject. A prism effect deflects the images to keep them centered on the film without the usual increase of the convergence angle on close range.

The attachment has flexibility and ease of operation. It offers the ophthalmologist an excellent adjunct to improved visualization for teaching and record purposes.

109 N. Wabash Ave. (2).

A Fixation Light for Tonometry and Tonography

S. I. ASKOVITZ, M.D., Philadelphia

The desirability of providing the patient with a fixation target during tonometry is well known. With the patient's eyes in a more or less steady position, the risk of corneal abrasion is minimized and the examiner may expect more trustworthy readings. For tonography examinations, proper fixation by the patient is all the more important.

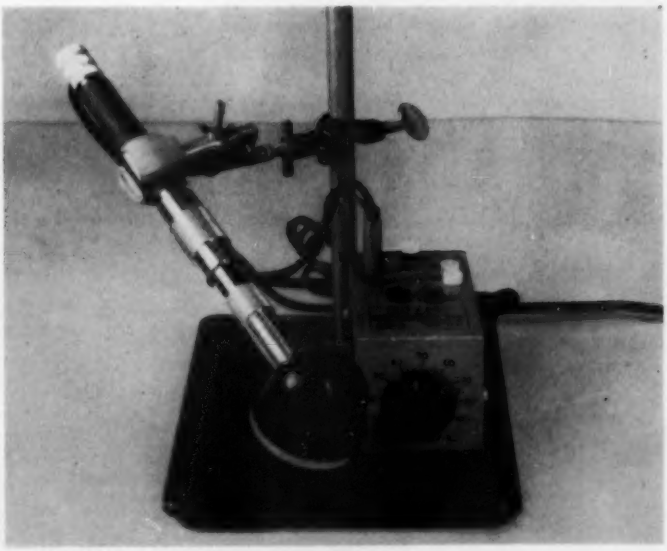
Some ophthalmologists have a small ceiling light mounted in their offices above the examining table. This is generally satisfactory, but it does not provide the flexibility which is often necessary in getting the patient to maintain the most desirable position of the eyes. In some clinics, a painted ball or other fixation target is held directly above the patient by means of an adjustable stand. This has the minor disadvantage that the fear of the object's falling may occasionally disturb a patient and interfere with relaxation.

After a number of possible arrangements were tried, a simple expedient, and one which is usually readily available, proved to be the most convenient * (Fig.). A streak retinoscope was supported by means of an adjustable clamp attached to an ordinary laboratory stand. By focusing with the sleeve of the retinoscope, it is possible to form a sharp image line on the ceiling at any distance, and the position of the light can be displaced or rotated at will.

Received for publication June 26, 1956.

From the Ophthalmology Research Laboratory (Dr. I. H. Leopold, Director), Albert Einstein Medical Center, Northern Division. The method described was developed during a study on tonography supported by a research grant from the Weinstock Fund.

* The instruments used were the Copeland Streak Retinoscope, Bausch & Lomb Optical Company, Rochester, N. Y., and the Port-A-Volt Transformer, Medico Instruments, Philadelphia 20.



Fixation light for tonometry and tonography.

FIXATION LIGHT

A portable transformer was used as the power source in order to avoid concern over failing batteries. The rheostat control is set to give adequate brightness, and the patient is instructed to concentrate upon the midpoint of the illuminated line on the ceiling. The presence of a small central scotoma in the fixating eye was found not to cause any difficulty.

If a stand is not available, the clamp may be attached to the shaft of a goose-neck lamp or the framework of a slit-lamp. Less conveniently, the retinoscope can be propped up against a few books or boxes or other support.

York and Tabor Roads (41).

Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

Orbitoethmoidal Osteoma

Orbitoethmoidal osteomata are relatively uncommon. Only 1 case of osteoma was found in 109 cases of tumors of the orbit studied by Reese in 1941. Forrest reported 5 cases among 184 primary orbital tumors collected from the registry of ophthalmic pathology. The outstanding features in our case are the presence of papilledema and the absence of all symptoms.

Report of Case

On July 19, 1954, a 13-year-old girl was brought for examination by her mother, who, for about six months, had noticed that the left eye had been gradually protruding (Fig. 1).

There was never any complaint such as headache or double vision. No history of head injury was present.

On examination, the most striking sign was proptosis of the left globe of a moderate degree. There was no difficulty in closing the eyelids. The periorbital structures, lids, and lacrimal apparatus did not show anything unusual. Ocular movements were full in all directions. On palpation of the orbital border a hard mass could be felt in the upper inner quadrant of the orbit, extending down below the internal palpebral ligament along the medial orbital border. It did not seem to have any connection with the eyeball. No abnormal pulsation was palpable or to be seen. No bruit was audible.

Vision of the right eye was 6/5 unaided. Vision of the left eye was 6/12; cc 6/9 with cyl−0.50 ax 180. The visual fields and blind spots were normal.

Radiological Examination (X-Ray Report by F. Zammit, M.D., D. M. R.).—Dense osteoma, ivory type, 2×2.25 cm., with regular structure and smooth round margins, arising from medial wall of the left orbit.

The medial surface of the osteoma, that is, its pedicle, shows a crenated, less dense

Received for publication June 28, 1956.

Figure 1

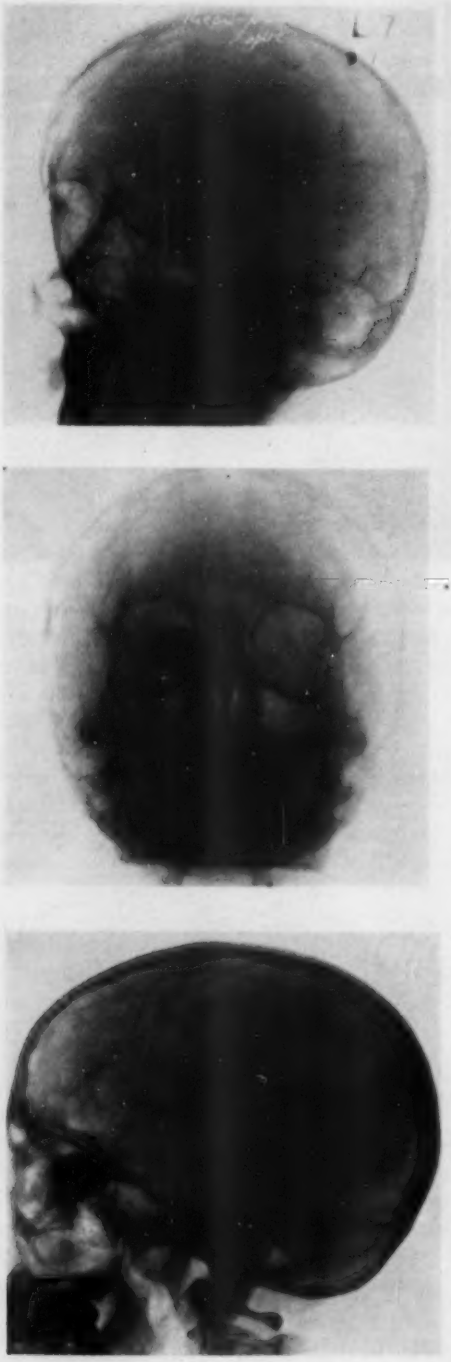


Figure 2

border and appears to originate from the region of the ethmoidal air cells, probably from the orbital plate of the ethmoid. From the lateral view, the growth of the osteoma appears to have spread upwards and backwards and has occupied the medial and posterior part of the orbital space. The adjoining structures show no abnormality, and there is no evidence of any pressure erosion. The sella is normal, and the frontal and ethmoidal air cells are normal.

Physical Examination.—Examination of the ear, nose, and throat did not show anything of unusual interest except for a slight degree of sinusitis. The temperature, pulse rate, and respirations were normal. General physical examination, including neurological examination, was completely negative.

Operation Procedure.—On July 22, 1954, the patient was prepared for a general anesthesia. An anterior orbital approach was decided upon, and an incision, similar to that used in performing a dacryocystorhinostomy, was made medial to the internal palpebral ligament and extending well below the latter to the lower orbital border. The periosteum was uncovered, incised, and reflected laterally along the whole length of the incision. No difficulty was found in displacing and protecting the eyeball from the field of operation.

A large pyramidal bony tumor was gradually uncovered and carefully isolated (Fig. 3). It appeared to arise, on a wide base, from the orbital surface (os planum) of the ethmoid, and it invaded the orbit to a considerable extent.

It was found necessary to use a chisel to fracture and dislocate the tumor at its base. The tumor was then grasped by a strong forceps, rocked from side to side, and gradually delivered out of the orbital cavity. Bleeding was astonishingly scanty, and the whole operative procedure was very smooth and simple.

There was no fusion of the tumor with the orbital contents and consequently no trauma to these parts.

Figure 3

The wound was closed by interrupted non-absorbable surgical (silk) sutures, and a gauze drain was placed at the lower extremity of the incision. At the end of the operation the proptosis had disappeared.

Postoperative Course.—For four days after the operation there was chemosis and swelling of the lids of the eye operated on. Swelling of the lids of the right eye was also noticeable. Penicillin was injected intramuscularly for 10 days. The drain was removed on the third day, and the sutures, on the seventh day. The cosmetic and functional results were entirely satisfactory. A radiological examination was made one month after the operation. Here is the report: "Osteoma completely removed. The central part of the medial wall of the left orbit is missing and there is some distortion of the left ethmoidal cells" (Fig. 4).

The patient was discharged on Aug. 2, 1954. She was kept under observation. A roentgenogram taken one year after the operation did not show any recurrence. Refraction performed at this time gave the following results: right eye, 6/5; left eye, 6/12; cc 6/9 with cyl−1.00 ax 180.

Figure 4

Examination of the fundus showed that the papilledema had disappeared.

Pathological Report (Dr. P. B. Schofield, Institute of Ophthalmology, London).—Macroscopic Examination: The specimen

consists of a partially lobulated tumor of hard bone with a thin covering of connective tissue. It measures approximately 25× 20×15 mm. and weighs 14.8 gm. After four months in nitric acid, the specimen is still not completely decalcified. The displacement of the specimen was 8 ml.

Section shows a benign nodule of dense, compact bone. The appearances are those of an ivory osteoma.

Comment

Osteoma of the orbit is really a disease of the paranasal sinuses extending into the orbit. According to Duke-Elder, an osteoma is an encapsulated bony tumor arising from disturbances or displacements of cartilage in the process of its development. The tumor originates from the paranasal sinuses and invades the orbit secondarily. The cells are stimulated into an osteogenetic activity by chronic infection or some unsuspected fracture. Fetissof (1929) suggested a periosteal origin of osteomas.

The frontal sinus is the commonest site of osteomas. Next in order of frequency follow the sphenoid, ethmoid, and maxillary sinus. Osteomas are divided histologically into two types (Parsons, 1905): (*a*) hard, or eburneated, 70%; (*b*) soft, or cancellous, 12%. There may be a mixed type consisting of a spongy center covered by layers of ivory bone.

Microscopical examination shows concentric layers of compact bone devoid of blood vessels. These tumors are covered by mucous membrane continuous with that of the paranasal sinuses. Osteomas grow very slowly over a period of years and usually start to show signs between 20 and 30 years of age; however, signs may become noticeable at an earlier age. Premonitory symptoms and signs may be present, such as swelling of the lids, chemosis, headache, neuralgia, epistaxis, and nasal obstruction.

Pain and diplopia are not outstanding features, and the tumor may reach large proportions, as in our case, without producing these signs. This is due to the slow rate of growth of the tumor. The capacity of the orbit is limited (adult female, 26 cc.), and as the tumor enlarges it acts as an expanding lesion. Eventually, it pushes the eye in front of it and produces exophthalmos. If treatment is not sought, severe pain, lacrimation, and lagophthalmos may follow (Rizzuti, 1951; McKibben and Casey, 1951).

An unusual sign in our case was a moderate degree of papilledema, probably due to direct pressure of the tumor on the optic nerve. The papilledema lasted for several months after the operation.

Though histologically benign, an osteoma may show malignant clinical characteristics if it is allowed to enlarge. According to Fetissof (1929), an osteoma is a neoplasm capable of unlimited growth. The tumor can perforate the dura, penetrate into the cranial cavity, and give rise to brain complications (Cushing, 1927).

It follows that, since one cannot foresee the tumors ultimate extension and destruction, early removal is indicated as soon as diagnosis is made.

The tumor can be surgically approached by three ways: (1) through the nose; (2) through the orbit by means of a cutaneous or conjunctival incision; (3) through the cranial cavity.

When it can be ascertained that the growth is restricted to the orbital cavity, one should prefer the orbital approach by means of a cutaneous or a conjunctival incision as near as possible to the area of growth (Sprowl, 1936; Rizzuti, 1951; McKibben and Casey, 1951). Cosmetic appearance is very good; scarcely any trace of the incision is left. It does not give rise to any functional disturbance. Our patient never complained of double vision and epiphora.

Summary

A case of orbital osteoma is reported. The following points are illustrated and discussed.

1. The growth of the tumor is slow and silent. It can assume large proportions before signs become evident. In our case, the most important signs were proptosis and papilledema.

2. After radiological confirmation of the diagnosis, it is important to operate as soon as possible in order to avoid complications and sequelae.

3. The nearest route to the area of growth is the best surgical approach to orbital osteoma.

F. J. DAMATO, F. R. C. S.
T. J. DAMATO, Central Hospital, Floriana, Malta.

BIBLIOGRAPHY

Cushing, H.: Experiences with Orbito-Ethmoidal Osteomata Having Intra-Cranial Complications, with Report of 4 Cases, Surg. Gynec. & Obst. 44:721-742, 1927.

Duke-Elder, S.: Text Book of Ophthalmology, Vol. 5, St. Louis, The C. V. Mosby Company, 1952, pp. 5596-5605.

Fetissof, A. G.: Pathogenesis of Osteomas of the Nasal Accessory Sinuses, Ann. Otol. Rhin. & Laryng. 38:404-420, 1929.

Forrest, A. W.: Intraorbital Tumors, Arch. Ophth. 41:198-232, 1949.

McKibben, B. G., and Casey, E. R., Jr.: Orbito-ethmoidal Osteoma, A. M. A. Arch. Otolaryng. 53:552-555, 1951.

Parsons, J. H.: The Pathology of the Eye, London, Hodder & Stoughton, Ltd., 1905, Vol. 2, pp. 745-747.

Reese, A. B.: Orbital Tumors and Their Surgical Treatment: Part 2, Am. J. Ophth. 24:497-502, 1941.

Rizzuti, A. B.: Osteoma of the Orbit, Am. J. Ophth. 34:49-52, 1951.

Sprowl, F. G.: Orbito-Ethmoidal Osteoma, with Report of a Case, Ann. Otol. Rhin. & Laryng. 45:886-890, 1936.

Annual Reviews

Cornea and Sclera

LEONARD CHRISTENSEN, M.D., Portland, Ore.

In this review the subject matter will be limited to the following selected fields of major interest.

Corneal Injury and Repair
- Tissue reactions
- Chemical reactions
- Toxic reactions

Keratoplasty

Infections
- Keratoconjunctivitis
- Herpes keratitis
- Tissue culture techniques
- Fungus infections

Medical Therapy

Sclera

Corneal Injury and Repair

Tissue Reactions

The ultimate aims in the management of corneal injuries are maintenance or restoration of normal structure and transparency. Loss of corneal transparency may follow any derangement of those factors which maintain relative deturgescence or alterations of the biochemical constituents of the intercellular ground substances or structural aberrations of the cellular system in the process of repair. This loss varies in time, intensity, and reversibility, depending upon which factor or combination of factors are affected.

Opacities following repair vary considerably depending upon the origin and characteristics of the reparative cells. Repair tissue may originate by regeneration of injured tissues, metaplasia of adjacent tissue, or remotely from cells of the reticuloendothelial system. It appears that better optical clarity is obtained in injuries repaired by direct regeneration of injured cells. For example, when injured corneal epithelium is replaced by regeneration of adjacent epithelium there is no appreciable impairment of optical qualities of the cornea. In contrast, Bowman's membrane is incapable of regeneration. When injured, it is usually replaced by fibrous connective tissue, which produces a leukoma. Repair tissue also originates locally through the phenomenon of metaplasia. Metaplasia may be considered as transformation of one normal cell to another of different properties, and it is usually stimulated by a pathologic process. The generalization may again be made that the greater the similarity in properties of the transformed cell to the original, the less intense the resulting opacity. For example, small tears in the anterior lens capsule can be sealed by fibrous connective tissue originating from metaplasia of the lens epithelium. The difference between the original epithelial cells and metaplastic fibrocytes is marked and the resulting opacity intense. This may have some bearing on corneal opacities resulting from stromal injuries. Corneal stroma is repaired by fibrocytic proliferation, and these fibrocytes may originate from normally existing adjacent keratoblasts, possibly corneal epithelium and endothelium, capillary endothelium, and tissue monocytes.[1,2] An observation has been made that cytologically identical fibroblasts may produce dissimilar ground substances in different tissues. The composition of the ground substance is vitally important in the optical properties of the cornea.[3,4] Hence, it is possible that in stromal repair less intense leukomas might occur where fibrocytic connective tissue originates from metaplasia of keratoblasts rather than connective tissue of other origin. Nevertheless, leukomas have been observed in corneal repairs where the

Received for publication Oct. 3, 1956.

regenerating connective tissue originated from keratoblasts.[5] From studies with an electron microscope an appreciable difference has been noted in the periodicity and diameters of collagenous fibers of normal corneal stroma from similar fibers in areas of cicatrization. This difference becomes less marked with the passage of time. No distinction was made regarding the origin of the repair fibers.[6]

Neovascularization of the cornea materially interferes with its optical properties. The pathogenesis of this complication has not yet been determined. After producing a series of corneal vascularizations in animals, one investigator arrived at the conclusion that stromal edema is a prerequisite. Neovascularization of central lesions occurred only if the surrounding edema reached the limbus, and a limbal or peripheral lesion was more readily vascularized because of the proximity of the edema to the limbus. Cortisone did not influence the edema or the subsequent vascularization. Attempts to decrease edema with hypertonic and hygroscopic agents such as glycerin and dextrose were successful but also inhibited repair, and greater scars resulted.[7]

Fibrin is an important factor in primary wound closure. It provides a mechanical seal that is an aid in the approximation of wound edges and may help prevent invasion of the anterior chamber by overlying epithelial cells. Inhibition of fibrin formation by administration of heparin or ethylbiscoumacetate (Tromexan ethyl acetate) not only delays, but may interfere with, wound healing.[8] However, the importance of fibrin cannot be solely attributed to the increase in tensile strength that its presence may add to a wound closure. In enucleated human eyes, the tensile strength of corneal wounds sealed with various concentrations of fibrin, blood plasma, and fibrinogen did not exceed 2 to 3 mm. of mercury.[9] Three phases of corneal wound healing were described following keratome incisions: a lag phase, a proliferative phase, and a plateau phase. In sutured limbal wounds, the immediate wound strength was found to be 6.5% of the undisturbed limbal tissue. No further increase in strength was noted for approximately three days, after which a gradual rise occurred to the ninth postoperative day. From the 9th to the 14th postoperative day there was a slight acceleration, and at the end of this period the wound strength measured 34% of that of the undisturbed limbus. Thereafter there was a gain of strength of approximately 1% per week. The wound strength curve was found to parallel fibrocytic proliferation.[10]

Postoperative striate keratopathy is a frequent complication of cataract surgery. The cornea undergoes considerable thickening the first few days after surgery, which then gradually diminishes. This thickening of the cornea is apparently due to an excessive intake of fluid and may be related to endothelial damage which, in turn, is enhanced by excessive manipulation in the anterior chamber during the operative procedure.[11] When corneal incisions are studied by ultraviolet light from a Woods lamp, loss of transparency becomes evident within 10 minutes. This change in transparency is not evident with the usual lighting methods. Within 24 hours, fluorescence is noted over the entire cornea, with the site of greatest intensity at the periphery of the wound. The intensity of fluorescence is proportional to the amount of manipulation during surgery. Regression is noted from the 3d day on and is usually complete after 15 days. This fluorescence is attributed to an infusion of new elements into the wound site, probably from blood which appears early at the upper site of the incision.[12]

Metaplasia of keratoblasts is not limited to the formation of collagen tissue. Observations on the mechanisms of nerve regeneration following injury indicate that polyblastic corneal cells are capable of forming sheaths of Schwannian cells through which neurofibrils regenerate.[13,14]

Chemical Reactions

A better understanding of altered tissue chemistry following corneal injury may be

the basis for more rational definitive future therapy. It must be appreciated, however, that pathologic chemical change is accompanied by cytologic damage. Any severe injury initiates a chain of biochemical and cellular responses that are probably irreversible despite any induced temporary reconstitution of the normal biochemical state. Therefore, therapeutic measures attempting to restore the chemical constituents alone are probably inadequate, since restoration of corneal transparency does not necessarily follow unless cytologic restoration also occurs.

Knowledge of the chemistry of the cornea is limited. The bulk of the cornea is composed of connective tissue which consists of two principal factors, a protein collagen and ground substance. The stromal lamellae are collagen and, in turn, are bound by ground substance. The ground substance is a gel supported by fibrillar or lamellar fabric consisting of proteins, mucopolysaccharides, and probably mucoids or glycoproteins. At the present time most investigations have been concerned with the mucopolysaccharides, which contain at least three known fractions, chondroitin, chondroitin sulphate, and keratosulphate. This latter term was coined by Meyer to designate the mucopolysaccharide peculiar to the cornea. Chondroitin has many properties similar to hyaluronic acid.[47] The mucopolysaccharide concentration in the cornea differs from that of the sclera as well as from the connective tissue of most other systems. In studies of radioactive sulphur uptake and elimination between corneal stroma and that of the sclera, the corneal uptake and elimination is slower. One explanation attributes this to the increased concentration of keratosulphate in the cornea.[15] At least four soluble corneal protein fractions have been found by electrophoretic studies in the corneal epithelium.[16,17] Descemet's membrane is a collagen tissue that differs from corneal stroma in morphology, swelling characteristics, solubility in acid, and in the type of polysaccharides.[18]

Of the chemical injuries, there are essentially two main types, those caused by acids and those caused by bases. Of the acids, hydrochloric, sulphuric, nitric, and carbolic are the commonest offenders. The severest injuries are caused by hydrofluoric acid and acetic anhydrides, since these latter two also exert a dehydrating effect on the tissue as well as a precipitation of corneal protein. Of the aklalis, the most common are caustic soda, potash lye, quicklime or slaked lime, and carbide. This type of burn is considered more dangerous. The effect of heat burn is similar to that of chemical except that the action of heat is circumscribed and heat burns are accordingly less injurious.[19] Apparently the toxicity of the commonest alkalis is related to the concentration of alkali rather than the nature of the cation, and severe corneal burns do not occur unless the pH is 11.5 or higher.[20,21] Common chemicals of this category include the hydroxides of sodium, potassium, calcium, barium, strontium, and ammonium. Other cations are toxic regardless of the pH and include certain dyes, beryllium, scandium, yttrium, and other rare earths. The pathogenesis of corneal opacities that develop following exposure to alkali is not known, but these opacities are most probably due to alterations of one or more of the stromal proteins. The possibility that these opacities are related to the binding of cation has been investigated. Binding is a term used to describe a poorly understood union between cations or anions to groupings on the protein molecules to which they have been exposed. An excellent review of this phenomenon has been presented by Gregor.[22] In rabbit corneas exposed to alkalis a progressive increase of bound cations occurred with increase of the pH, and the rate increased sharply at pH of 10.5 to 12. At near neutral the cations were bound mostly by mucoid of the cornea, but at the injurious range most binding occurred with collagen. Intense opacities and extensive binding of calcium was observed in rabbit corneas exposed to calcium hydroxide. However, cor-

neal stroma exposed to 10% calcium chloride was not appreciably altered despite an equal increase in concentration of calcium. The role that binding plays in corneal opacities following chemical burns remains to be determined.[23] When excised corneas were immersed in sodium hydroxide a rapid swelling was noted, and the rate of swelling was related to temperature and concentration of the solution. The swelling was thought to be due to imbibition of water by stromal proteins.[24] The intensity of opacities in the corneas of rabbits following exposure to 5% and 10% caustic soda was found to vary with concentration, extent, and duration of contact. In all cases a connective tissue membrane developed on the posterior corneal surface.[25]

Corneal opacities following chemical burns may be related to peripheral nerve damage as well as alteration in the chemistry of the ground substance. When the ciliary ganglion was blocked by procaine (Novocain) less destruction and less intense leukomas were noted in the corneas of rabbit eyes exposed to ammoniates and sulphuric acid than in control animals. Clinical treatment of alkali and acid burns by procaine block was reported as beneficial.[26]

In corneal injuries following instillation of hydrochloride acid, the ascorbic acid content was found to be significantly decreased immediately after injury. This remained lower than the controls for approximately 120 hours. Similar burns by hydrochloric acid on corneas of enucleated rabbit eyes did not show any appreciable alteration in ascorbic acid concentration from the normal. From these findings the authors assumed that in vivo the ascorbic acid was not destroyed but rather released from its bound site in the cornea and washed away during the burning procedure. The relationship of loss of ascorbic acid to degree of injury was not determined.[27]

In a histochemical study of rabbit corneas injured by surgical incision, compounds containing sulfhydryl groups increased considerably in the multiplying epithelium and adjacent stroma early in the stage of stromal healing. Ribonucleic acid also increased in concentration in the regenerating stroma and epithelium. In contrast, deoxyribonucleic acid changed very little. Phosphatase increased in the areas of vascularization, and this increase was attributed to the influx of new vessels.[28] Sectioning of the ciliary vessels and nerves and optic nerve in rabbits was followed shortly by keratitis. A diminution of corneal mucopolysaccharides was noted.[29]

When a tissue deficiency of ascorbic acid exists, some delay in wound healing may occur. Since the concentration of ascorbic acid is less in an aphakic eye, the rate of wound healing following heat injury was compared in phakic versus aphakic globes. Corneas in the aphakic eyes required 40% longer time for healing than the controls. The ascorbic acid content of the cornea and aqueous of the aphakic eyes was found to be considerably lower than that of the controls.[30]

Toxic Reactions

Because of its exposed position and sensitivity, the corneal epithelium is particularly susceptible to injury. Such superficial injuries usually are manifested by a photophobia, corneal irritation, and conjunctival hyperemia. Hexachlorophene (pHisoHex), a useful bactericidal agent for preoperative preparation of the skin, may induce a keratitis when instilled into the conjunctival sac. In rabbits, a severe keratitis associated with loss of epithelium and stromal swelling rapidly developed following instillation of this medication. Toxicity was attributed to an ingredient of the preparation used, trinitrotoluene.[31] Corneal epithelial damage was found following repeated instillations of surface anesthetic ointments and solutions in the conjunctival sac. Such agents appreciably inhibited regeneration of corneal epithelium and consequently prolonged healing time. Following repeated instillations, the anesthetic effect was gradually lost, and when the agent was administered long enough corneal erosions occurred. The gen-

esis of these lesions was thought to be corneal nerve damage.[32,33] Exposure of corneal epithelium to butyl alcohol vapor was followed by photophobia and epiphora. The integrity of the corneal surface epithelial cells was maintained, but innumerable small vacuoles were noted in the deeper strata.[34] Repeated exposures to hydroquinone, an ingredient of a photographic developer, led to a serious impairment in vision. The cornea and conjunctiva within the palpebral fissure developed a characteristic pigmentation and alterations in the structural arrangement of the cornea. Vertical folds appeared in Descemet's membrane, and an irregular progressive astigmatism developed. Eventually ulcerations and vascularizations occurred.[35] Bilateral epithelial keratitis was observed in 14 patients following several weeks administration of isoniazid and amithiozone. The lesions consisted of numerous intraepithelial vesicles.[36]

Keratoplasty

The dramatic evolution, current problems, and present status of keratoplasty are best summarized in two excellent texts that have recently appeared.[37,38] Particularly gratifying optical improvements have been achieved for such disorders as keratoconus, some dystrophies, and circumscribed central leukomas.[39] However, the limited success attained in Fuch's dystrophy and scarred vascularized corneas has been disappointing.[40] Because of this latter group and because of need for over-all improvement, many of the efforts of more recent years have been devoted to refining techniques. Most efforts have been directed toward solution of difficult facets of major problems that have, as yet, remained largely unsolved. These problems include the clouding of grafts, better storage of donor material, wider application of keratoplasty, use of prosthetics, and better control of undesirable tissue reaction to injury.

A particularly baffling and frustrating problem is the inexplicable clouding of grafts that occasionally occurs. Such clouding may appear shortly after a surgical procedure or may be delayed for several months. The intensity of clouding is variable and frequently reversible. Opinions vary widely concerning the pathogenesis of this complication. Undoubtedly it is related to such factors as the age and state of the donor and recipient cornea, improper fixation, biological factors, endothelial damage, and such postoperative complications as synechias, uveitis, and increase in intraocular pressure. Technically, an ideally positioned graft presumes exact approximation of each tissue plane of the donor to its counterpart in the recipient. Such an ideal can be achieved only by perfect sectioning, placement, and fixation, none of which is consistently obtainable by present methods. Since much of the success of keratoplasty hinges on these technical phases, there is a constant search for improvement.[41-43] Most attempts to improve fixation rely on various methods of splinting with either prosthetic or tissue splints. Such splints are usually modifications of similar devices introduced in the past. A contact lens was modified with appropriate perforations to allow for suturing to the recipient cornea in three areas. Other perforations permit flow of secretions. Tissue sections of grafts fixed by this method in experimental keratoplasty demonstrated good wound approximation, fibroblastic proliferation, and cellular infiltration in the wound area. The advantages claimed for this technique include simplicity, ease and speed of application of sutures, ease of removal of sutures, good approximation, and absence of radiating corneal leukomas. Experience with this type of splint has been limited to animals.[44] Another method of splinting advocates fixing the graft with an overlying rabbit cornea. The rabbit cornea was sutured over the graft to the peripheral recipient cornea, with no sutures between the graft proper and recipient cornea. Swelling and opacity of the rabbit cornea was prevented by lyophilizing the structure after formalin fixation. After 138 transplantations using various methods of fixation,

splinting with rabbit cornea was considered superior. Of 48 transplantations using this method, transplants of 5 mm. in diameter healed completely. No mention was made of the exact optical results or the percentage of success with 7 or 8 mm. grafts.[45]

In order to minimize exposure of the recipient anterior chamber and facilitate placement of the grafts, a method of corneal suturing has been advocated whereby it is possible to preplace four sutures in the donor and recipient corneas. A partial penetrating incision is made in the donor cornea, and four sutures are inserted. These sutures are then threaded through the trephine, after which the corneal disc is removed. The same sutures are inserted in a preformed groove in the recipient eye in the corresponding four quadrants and are held aside until the corneal disc has been removed. The graft is then drawn into position. Greater safety and better approximation of the wound edges in penetrating transplants is claimed.[46]

Several investigators have been concerned with the irregularity of the cut surface and endothelial damage to both the recipient and donor corneas following the usual methods of trephination. The integrity of Descemet's membrane and endothelium has been considered an essential factor in the retention of corneal transparency, since poor approximation and large dehiscences in the endothelium may contribute materially to subsequent opacification.[47] During incision of the cornea by the usual methods of trephination the contour of the cut edge has been found to vary appreciably with the wide alterations in intraocular pressure. By maintaining a constant and equal intraocular pressure in both the donor and recipient eye more uniform sections may be obtained. One method consists of injecting physiologic saline into the anterior chamber under a constant pressure head. In all but 1 of 18 trephinations performed on rabbit eyes by this method a uniform complete disc of corneal tissue was excised.[48,49] Another method of obtaining a more uniform section utilizes a punch introduced through a peripheral incision. This punch has been modified to correct for disadvantages of its predecessors. With limited experience the results are reported as gratifying.[50]

Biological factors, including the antigen-antibody reaction, undoubtedly participate in the pathogenesis of clouding of corneal grafts. The extent of this participation remains unknown, and during the past year few contributions have been made in this phase of research. However, ample evidence has been offered in related fields that antibodies play an important role in the rejection of homografts.[51-55] Some additional data have been presented of a similar mechanism in corneal transplantation, but no new conclusions have been drawn.[56-58]

Vascularized scarred corneas account for a moderately high incidence of blindness due to corneal disease. This problem may become more prevalent with expansion of industry and the consequent increase of chemical burns. At the present time keratoplasty directed at optical improvement for this type of corneal opacity is not much more successful than it was several decades ago. Adjunctive measures such as irradiation have been of little benefit where vascularization is well established, because there is no regression of the larger vessels.[59-61] It is questionable that the advantages of irradiation outweigh the disadvantages, because of the deleterious effect on the lens and inhibition of wound healing. The inhibitory effect on wound healing was amply demonstrated in a study on rabbit corneas. Histologic examination of wounds in corneas previously irradiated with dosages ranging from 1250 r to 40,000 r demonstrated inhibition of normal fibroblastic (keratoblastic) proliferation at the wound site. In some instances only epithelium bridged the wound surface. Poor wound healing of the irradiated corneas was evident as long as six months after surgery. When 27,000 r to 40,000 r had been administered as long as two years prior to the surgery a similar fibroblastic inhibition was noted. Moderate dosages of irradiation administered immediately before surgery and

as long as three months prior to surgery inhibited wound healing to a similar degree. The clinical implications are self-evident.[62] Prophylactic or therapeutic medications have been equally ineffective against revascularization of grafts. Corticosteroids have been observed to inhibit neovascularization initially, but the final results have not been greatly modified.

Two unrelated observations have been made that may have an important implication in the future surgical treatment of vascularized corneas. First, surface vessels in contrast to deep interstitial vessels are most difficult to control, because surface vessels exhibit greater vitality. Interstitial vessels have less capacity to penetrate a graft and prognosis for successful keratoplasty is correspondingly increased when vascularization is limited to the stroma.[63] Second, where surface vascularization exists a lamellar graft will often remain free of surface vessels because the vessels regenerate between the wound surfaces. Thus the interface between the graft and recipient cornea will be vascularized, leaving the outer surface free. Advantage has been taken of the above observations to devise a new surgical approach. The principal of the procedure consists first of providing a more normal bed for a penetrating graft and simultaneously diverting the surface vessels into the corneal substrate, where their vitality is greatly reduced. This initial step is accomplished by installation of a 6 mm. central lamellar graft. If this graft remains clear, an annular peripheral lamellar graft is inserted between the 7 and 9 mm. circumference, leaving a 1 mm. strip of undisturbed recipient cornea between the two grafts. By this means the surface vessels are diverted to the interface between the annular graft and recipient cornea and are blocked by the 1 mm. ring of recipient cornea that separates the two grafts. If the second graft remains clear, a third 5 mm. penetrating graft is placed in the original central lamellar graft. This penetrating graft is now installed in a more normal bed, and the number of vessels regenerating across its surface is reduced to a minimum. This operation was performed on three patients with severe vascularization of the cornea. The results are reported as excellent.[64,65] Another method advocated a wide keratectomy and installation of a peripheral lamellar graft to the recipient cornea. The central portion remains uncovered and subsequently reepithelializes. Regeneration of the central corneal stroma occurred under the new epithelium, and in a few months the cornea became nearly normal in curvature. This technique was applied to 20 eyes severely injured from burns with hot metals, acids, and alkalis, 16 of which required plastic repair for symblepharon prior to keratoplasty. In most cases the visual acuity improved from light perception to finger counting, and in some a little more. The optical results were considered better than those obtained with penetrating keratoplasty.[66]

Keratoplasty for Fuch's endothelial and epithelial dystrophy has been considered hopeless. However, successful transplantation has been reported when the endothelial degeneration is limited to the central portion of the cornea.[67] In advanced Fuch's dystrophy and aphakia a heroic technique has been described for posterior lamellar keratoplasty. The anterior portion of the donor cornea was excised and discarded. The posterior cornea was then removed. In the recipient eye a keratome incision was made into the anterior chamber and the posterior half of the cornea was undermined with a corneal knife. Excision was completed with scissors. The donor graft was inserted and secured at three sites by double-arm sutures. The peripheral corneal incision was then closed. Visual acuity improved from 1/200 to 5/200, but, following onset of glaucoma, it again dropped to 1/200. The postoperative period was marred by several antiglaucoma surgical procedures, which may have interfered with the final result. The graft remained in good position and the cornea was free of edema after one year, but no

further improvement in visual acuity was noted.[68]

Therapeutic lamellar keratoplasty was successful in two of three patients with chronic corneal ulcers.[69] A lamellar keratoplasty with use of a lyophilized donor cornea was performed for an extensive vascularized pterygium. The result was reported as excellent.[70]

Implantation of inorganic transparent materials dates back 100 years. Rock crystal, glass, methacrylate (Plexiglas), celluloid, and acrylic corneal implants have been used, and with few exceptions results have been discouraging. A major factor has been the inability to fix the implant by proliferation of fibrous connective tissue in desirable sites. A unique modification of previous methods consists of excising a disc of outer cornea and inserting a small methacrylate disc into a trephine opening through the posterior cornea. The anterior corneal disc is then resutured over the implant. Six weeks after the initial step the cornea covering the disc is trephined and removed. By this time the prosthesis is firmly fixed in position by scar tissue. Of 28 surgical procedures in rabbit eyes, 6 were reported as clear initially. However, in the favorable group a membrane gradually covered the posterior corneal surface in four to five months. In 12 others the posterior surface of the disc was found to be covered by an opaque grayish-white membrane on removal of the anterior flap. The authors conclude that the principal problem is formation of fibrous connective tissue behind the foreign body. Their attempts to correct this have been unsuccessful to date. They feel that the procedure is encouraging and warrants further investigation.[71] Another approach consists of first implanting a disc into the sclera. Subsequently, this disc and its surrounding sclera are implanted into the cornea, but eventually the disc sloughs.[72]

To summarize the statistical results of large series of cases is not within the scope of this paper. However, the results of several large series have been reported during the past year, and in general the statistical findings are comparable with presently accepted figures.[73-75]

One of the major obstacles in the evolution of keratoplasty has been the lack of suitable donor material. The establishment of eye banks following Filatov's demonstration that cadaver corneas are adequate greatly enhanced its development, but there are many problems related to obtaining and preserving donor material.[76] Even at the present time the limited storage life of corneas reduces the effectiveness of eye banks, since more donor eyes are discarded than are used. Degenerative changes are histologically evident as early as 24 hours after enucleation.[77] Rapid deep freezing of corneas in aqueous solutions has been unsuccessful because of loss of viability of the tissue. However, when corneas have been stored in 15% glycerin and saline at subfreezing temperatures viability has been retained. Glycerin apparently prevents cell damage from crystallization of water. Successful grafting has been reported with the use of corneas stored by this method over a prolonged period of time. In cats successful grafting has been performed with corneas stored in 95% commercial glycerin for one month at 4 C, although a stormy postoperative course ensued.[78-80]

Infections

Keratoconjunctivitis

Early in World War II several epidemics of acute keratoconjunctivitis first appeared in the shipyards of the West Coast. The disease later spread over the entire continent, and since then there have been many sporadic outbreaks over the world including several during the past year.[81-85] The great majority of cases have presented common clinical symptoms and findings that labeled it as a new disease entity of importance. The principal signs and symptoms consist of bilaterality, photophobia, translucent edema of the lids, marked conjunctival injection, diffuse watery discharge, tender preauricular lymphadenopathy, and superficial dissemi-

nated corneal infiltrates. The rapid dissemination of the disease indicated an infectious etiology, which was later identified as a filterable virus.[86] However, doubt now exists that the virus first reported was the specific cause or that any one group of viruses is the sole causal agent.[87-89] In 1954 a new virus series labeled adenoidal-pharyngeal-conjunctival (APC) agents was isolated, and it has since been found capable of producing keratoconjunctivitis. By serologic and tissue culture methods at least six strains were initially isolated, of which Types 1, 2, 5, and 6 were recovered from the tissue cultures of adenoids and tonsils. Type 3 was recovered from cases of acute febrile pharyngitis with conjunctivitis, and Type 4, from acute febrile respiratory disease. Important distinguishing features of this group of viruses include a characteristic cytopathogenic effect produced in the tissue cultures and production of a soluble complement-fixing antigen shared by all immunologic types. Initially only Type 3 was thought capable of producing conjunctivitis, and of the original six strains none appeared capable of producing keratitis. However, in the past two years several reports have appeared presenting evidence that corneal involvement does occur and that clinically the disease simulates epidemic keratoconjunctivitis to a variable degree. The APC virus was established as the causal agent through demonstration of neutralizing antibodies.[90-94] Further investigation established that serum obtained from four patients with epidemic keratoconjunctivitis in the Windsor epidemic of 1951 and from two patients with epidemic keratoconjunctivitis in Toronto in 1954 had neutralizing antibodies to a newly found strain, Type 8 APC (Trimborn), which was first discovered on the West Coast.[95] This new strain has been labeled the Jawetz virus.[96] Similar viruses have been recovered from tissue cultures in England, and neutralizing antibodies against APC virus have been found widely distributed in the north of England.[97] At the present writing confusion exists regarding the relationship of the EKC virus or viruses to APC virus, but it is evident that there are multiple etiologies to the clinical syndrome of epidemic keratoconjunctivitis.

Herpes Keratitis

The role of immunity in herpetic keratitis has been of some interest. After an infection immune bodies may appear systemically in the circulating blood serum and locally in the involved tissue. The mechanism of local immunity is not understood. The observation has been made that a high serum antibody appears within four weeks after infection and persists for several months. This serum antibody concentration in rabbits provides minimal protection against reinfection but ameliorates the progress of the disease where reinfection occurs. In contrast, local immunity offers a high degree of protection against reinfection.[98] A similar observation has been made for the related vaccinia virus when the serum antibody reaches moderate levels. Hyperimmunization of rabbits following intravenous injections of live vaccinia virus increases the protection slightly. The highest degree of immunity is produced by subconjunctival injections and by active vaccinia keratitis. Local tissue immunity persists for a short period after the serum antibody has fallen to low levels.[99]

In a discussion of the pathogenesis of herpes simplex and other related corneal disturbances the relationship of virus infection to trauma has again been emphasized. These observations tend to confirm the strong suspicion that viable herpes viruses are dormant in the tissues of a large number of normal persons.[100,101]

A clinical study of the alterations of corneal innervation in herpes simplex by staining with methylene blue indicated that the initial changes in the nerve fibers consist of a spindle-shaped thickening of some of the fibers of the nerve stem and fragmentation of the fibers. These changes are followed by hyperregeneration of several nerves and subsequent ramifications of

hypertrophic stems and loops. In newly formed bundles varicosities have been observed.[102] Microscopic studies of the tissue changes in herpetic keratitis in rabbits show typical intranuclear inclusion bodies in many epithelial cells, necrosis of epithelial cells, and edema and vesiculation of the deeper layers of the affected area. Mitotic figures and nuclear alterations are common, and pathologic changes are often noted in the stroma. Stromal changes consist of degeneration and proliferation of the fixed cells of the cornea, degeneration of the lamellae, immigration of lymphocytes and leukocytes between the lamellae, and severe damage to nerve bundles.[103,104]

The search for an effective therapeutic drug in the treatment of herpes simplex virus continues. Cortisone is believed to enhance the spread of herpetic infection of the cornea by inhibiting the inflammatory tissue reaction to infection. An observation has been made that the somatotropic hormone (STH) has the opposite tissue effect and tends to stimulate allergic and inflammatory reaction.[105] Hence, if instillation of cortisone enhances the spread of infection in the cornea, STH theoretically should have an inhibitory effect. Following inoculation of rabbit corneas with herpes virus, STH was given both therapeutically and prophylactically by subconjunctival injections and drops. Comparison with controls indicated that STH was ineffective therapeutically but that prophylactically it might have some inhibitory effect. A similar study of desoxycorticosterone acetate (Doca), estrogenic hormone, and androgenic hormone gave the same negative findings. Influenza vaccine was subjected to the same study, since successful clinical experiences in controlling herpes zoster infections with this vaccine have been reported.[106] No beneficial effect was noted. A new antibiotic (O. C. 1315-262, Sharpe & Dohme) has been found to be of little benefit.[107]

Irradiation of the cornea is reported as an effective therapy for dendritic ulcer. Claim is made that the inflammatory reaction subsides rapidly and is not followed by desquamation of the epithelium and that recurrences of corneal lesions are rare.[108] Some rationale for irradiation therapy has been offered by the following observations. Apparently elaboration of antibody is not limited to certain specialized cells, as was originally considered to be the case, and, among the other tissues, may be produced by epithelium. Local immunizing antibody production has been found to be enhanced by irradiation.[109,110]

Tissue Culture Techniques

In the discussion of the above viruses, mention is made of tissue culture techniques. This method of demonstrating active virus infection of the cornea has become increasingly important as a diagnostic and research aid. Epithelial cells are hardy and with proper cultural methods will proliferate and form sheets over a surface. Advantage is taken of the fact that viruses invade epithelial cells and that, following their invasion, characteristic cytopathogenic alterations occur. Usually the cells are obtained from human or animal kidney, corneal epithelium (rabbit), and carcinoma cells originally obtained from carcinoma of the cervix (HeLa cells). When these epithelial cells are exposed to viable viruses cellular invasion occurs and, in addition to specific cytologic alterations, disintegration of the sheets becomes manifest microscopically. The possibilities of tissue culture as a more rapid and sensitive diagnostic test for herpes simplex have been investigated. Rabbit corneal epithelium, HeLa cells, and human kidney epithelium cultured in standard media have been inoculated from a prepared solution of washings and scrapings obtained from active herpetic lesions. In stained preparations of rabbit corneal epithelium recognizable signs of infection are evident as early as six to eight hours after inoculation. The cellular changes consist of nuclear inclusions and marginations of chromatin and early degenerative changes in the epithelial sheets. Stained preparations of infected HeLa cul-

tures show changes in approximately 15 hours, and by 30 hours there is partial disintegration of the sheets of cells. In human kidney epithelium nuclear inclusions and giant cells typical of herpetic infection are found. A survey was made of 20 cases of suspected herpetic infections of the skin, mouth, and eyes in order to compare the results of tissue culture methods with the standard method of inoculating corneas of live rabbits. Of the 20, there were characteristic changes in tissue culture in 13, compared with 11 of the inoculated corneas. However, of 10 specimens collected from typical cases of dendritic keratitis, virus was recovered from only 5. The authors could not explain this discrepancy. The greatest advantage of the tissue culture method is time, as indicated by 7 hours necessary by this method versus a minimum of 10 days for in vivo studies. There is also an indication that it may be more sensitive.[111]

Fungus Infections

Fungus infections of the cornea should be suspected in chronic hypopyon ulcers that have received repeated local instillations of antibiotics or corticosteroids.[112] These infections may occur because of contamination of the medication instilled, or the biological effect of the medication may permit overgrowth of fungi normally present in the conjunctival sac. Fungi were cultured from the conjunctival sac of 18% of normals compared with 67% of patients previously treated with cortisone or hydrocortisone. Hydrocortisone solution was instilled in the conjunctival sac of 18 persons in whom no fungi had been previously demonstrated. After 14 days of therapy fungi were found in 9. One fungus identified was Candida albicans.[113]

Medical Therapy

A most striking demonstration of endocrine influence on wound healing has been observed following administration of corticosteroids. Despite the wide application of these drugs, their mechanism of action still remains speculative. The concentration of cortisone and hydrocortisone labeled with C^{14} in the corneal stroma and aqueous has been found to be remarkably low after administration to the cornea.[114]

Hydrocortisone has a less marked inhibitory effect on the regeneration of corneal epithelium than cortisone but, like cortisone, inhibits fibrocytic reaction.[115] An attempt has been made to block the inhibitory reaction of hydrocortisone on regenerating corneal epithelium following injury by adding chlorophyll to the hydrocortisone solution. The rate of epithelial repair is appreciably advanced when chlorophyll is added to the solution, in comparison with the results in injured eyes treated with hydrocortisone alone.[116] This inhibiting effect of the corticosteroids is only temporary and does not alter the ultimate uncomplicated wound repair.[117] There are no appreciable differences in the inhibitory effect of cortisone given locally in the form of drops versus cortisone given by subconjunctival injection.[118] Local instillations of cortisone and hydrocortisone ameliorate the symptoms of keratoconjunctivitis sicca but do not alter the physical findings of this disease. Administration of corticotropin systemically is no more effective than use of the local preparation.[119]

Of the newer corticosteroids, prednisone (Meticorten) and prednisolone (Meticortelone) are the most promising. These agents are more effective than cortisone (Cortone) or hydrocortisone (Hydrocortone) when used either locally or orally, and equivalent dosages have fewer side-effects. The indications and contraindications for the use of these drugs remain the same as for cortisone and hydrocortisone.[120-122]

The monoethyl ether of ethylene glycol (Ethylcellosolof) increases the effectiveness of antibiotics in local instillation. It may act by enhancing the concentration of the drug in the deeper tissues of the cornea.[123] Chelating agents have been defined as compounds which form soluble complexes with specific metals or other compounds and remove them from the chemical milieu in

which they occur.[124] Such an agent, ethylenediamine-tetraacetic acid, has been used effectively for the removal of corneal calcium deposits of band keratopathy. This compound forms a soluble complex with the calcium deposited in the corneal stroma and is washed away. A similar agent, Versenate, the disodium salt of ethylenediaminetetraacetic acid, has been reported equally effective. It is instilled in a similar manner, drop by drop on an abraded cornea for 15 minutes. During instillation clearing of the cornea becomes evident.[125]

Instillation of a combination of streptokinase and streptodornase (Varidase) may be beneficial in the treatment of severe corneal ulcers. This medication probably promotes the clearing of necrotic debris from the surface of the ulcer, which may permit better exposure to other medications. The optimum dosage consists of five to six daily instillations of solutions ranging from 2000 to 10,000 units per cubic centimeter.[126]

Eritrocilline, a combination of lyophilized human erythrocytes and penicillin, has been reported as more effective than penicillin alone for experimental corneal abrasions in rabbit eyes.[127]

An important single factor in the control and treatment of endemic trachoma is a sanitary environment. When this was coupled with administration of chloramphenicol, chlortetracycline (Aureomycin), and oxytetracycline (Terramycin), excellent results were obtained in mass treatment of a heavily infected area.[128] Of the various therapeutic agents, sulfacetamide remains the drug of choice. Only minor benefit has been reported with chloramphenicol, oxytetracycline and chlortetracycline.[129] Oral and local administration of tetracycline is beneficial, particularly for trachomatous keratitis, but not as effective as the sulfonamides. It may be of value as a substitute for the latter.[130]

Sclera

Confusion seems to exist regarding the nature of a focal inflammatory lesion of the sclera termed scleromalacia perforans. Scleromalacia perforans was originally considered an ocular disease of obscure etiology manifested by a localized circumscribed perforation of the anterior sclera. Typically it occurs in older people, some of whom have had rheumatoid arthritis of long duration. The occasional absence of a clinically evident inflammatory reaction has led to the conclusion by some that it is a purely degenerative process. However, similar circumscribed perforations of the anterior sclera have also been noted following focal inflammatory reactions of the sclera or limbus with or without rheumatoid arthritis. Histologically these latter lesions closely resemble rheumatoid nodules appearing elsewhere on the body, and in these instances the relationship to rheumatoid arthritis has been well established. The suggestion has been made to reserve the term scleromalacia perforans for noninflammatory scleral dehiscences that occur in persons with chronic rheumatoid arthritis. This is to distinguish it from another entity, necroscleritis nodosa, which is inflammatory and occurs in the absence of rheumatoid arthritis.[131] Scleromalacia perforans is also distinguished from nonperforating scleromalacia and scleromalacia with porphyrinuria.[132] Lesions simulating scleromalacia perforans were described as occurring in a patient with chronic rheumatoid arthritis, splenomegaly, and leukopenia (Felty's syndrome). Following a seige of episcleritis a focal slough of the sclera occurred, leaving a dehiscence of the sclera and exposing the uvea. A corneal ulcer subsequently developed and perforated, which was followed by loss of the eye.[133]

The above cited reports imply that scleromalacia perforans is a specific clinical entity that is to be distinguished from similar-appearing lesions of slightly different clinical manifestations. However, there is no uniformity of opinion regarding which of these lesions is to be designated scleromalacia perforans. At the present time it appears that any rigid classification

is not logical until more is known of the pathogenesis of the disease.

3181 S. W. Sam Jackson Park Rd. (1).

REFERENCES

1. Gunther, G.: Corneal Regeneration, Wiss. Univ. Greifswald 4:107-110, 1954-1955.

2. Binder, R. F., and Binder, H.: Experiments on Wound Healing in the Endothelium of the Cornea, Am. J. Ophth. 41:861, 1956.

3. Meyer, K.: The Chemistry of the Ground Substances of the Connective Tissues, Acta XVII Conc. Ophth. (1954) 1:470-474, 1955.

4. Woodin, A. M.: Interaction between Proteins and Mucopolysaccharides in the Cornea, Acta XVII Conc. Ophth. (1954) 1:475-482, 1955.

5. Grigorieva V.: Experimental . Histologic Study of the Process of Healing of Wounds of the Cornea, Vestnik oftal. 34:11-17, 1955.

6. Garzino, A.: Collagen Fibers in the Normal Cornea and in Cicatricial Processes, Rass. ital. ottal. 24:118-157, 1955.

7. Heydenreich, A.: Corneal Vascularization in Animal Experiments, Klin. Monatsbl. Augenh. 127:465-471, 1955.

8. Binder, R., and Binder, H.: Experimental Investigations into the Effect of Anticoagulants on the Healing of Corneal Incisions, von Graefes Arch. Ophth. 155:337-344, 1954.

9. Kalfus, T.: Consolidation of Corneal Wounds by Fibrin, Ceskoslov. oftal. 11:135-138, 1955.

10. Gliedman, M. L., and Karlson, K. E.: Wound Healing and Wound Strength of Sutured Limbal Wounds, Am. J. Ophth. 39:859-866, 1955.

11. Giardini, A., and Cambiaggi, A.: Recherches sur l'épaisseur cornéene àpres extraction de la cataracte, Ophthalmologica 131:41-50, 1956.

12. Renard, G., and Bouzas, A.: Contribution a l'étude des troubles de la cornée par l'examen à la lampe de Wood, Arch. opht. 15:693-704, 1955.

13. Reiser, K. A., and Colmant, H. J.: Experimental-Histological Studies Concerning the Change in the Corneal Nerve Apparatus in Keratoplasty: I. General Survey of the Processes of Degeneration and Regeneration, von Graefes Arch. Ophth. 157:314-355, 1956.

14. Vrabec, F.: Relations Between Keratoblasts and Nerve Fiber Regeneration in the Cornea, Ophthalmologica 130:24-31, 1955.

15. Dohlman, C. H., and Boström, H.: Uptake of Sulphate by Mucopolysaccharides in the Rat Cornea and Sclera, Acta ophth. 33:455-461, 1955.

16. François, J., and Rabaey, M.: Les Protéines de l'épithélium cornéen, Bull. Soc. belge opht. 108:641-652, 1954.

17. François, J., and Rabaey, M.: Les Protéines de l'épithélium cornéen, Ann. ocul. 189: 445-458, 1956.

18. Dohlman, C., and Balazs, E.: Chemical Studies on Descemet's Membrane of the Bovine Cornea, Arch. Biochem. & Biophysics 57:445-457, 1955.

19. Pillat, A.: Problems in the Treatment of Burns of the Conjunctiva and Cornea Caused by Chemical Agents and Heat, Eye Digest 1:3-13, 1956.

20. Hughes, W. F., Jr.: Alkali Burns of the Eye: I. Review of the Literature and Summary of Present Knowledge, Arch. Ophth. 35:423-449, 1946.

21. Friedenwald, J. S.; Hughes, W. F., Jr., and Herrmann, H.: Acid-Base Tolerance of the Cornea, Arch. Ophth. 31:279-283, 1944.

22. Gregor, H.: The Specific Binding of Ions by Polyelectrolytes: Correlation with Biological Phenomena, Tr. New York Acad. Sc. 18:667-692, 1956.

23. Grant, W. M., and Kern, H. L.: Action of Alkalis on the Corneal Stroma, A. M. A. Arch. Ophth. 54:931-939, 1955.

24. Shapiro, H.: Swelling and Dissolution of the Rabbit Cornea in Alkali, Am. J. Ophth. 42: 292-298, 1956.

25. Konrad, A.: Experimentally Produced Corneal Leucoma in Rabbits, Wiss. Univ. Freifswald 4:105-106, 1954-1955.

26. Khasanova, N.: The Neurological Factor in the Pathogenesis of Chemical Burns of the Eye, Vestnik oftal. 34:12-17, 1955.

27. Guidry, M.; Allen, J., and Kelly, J.: Some Biochemical Characteristics of Acid Injury of the Cornea, Am. J. Ophth. 40:111-119 (Nov., Pt. 2) 1955.

28. Krwawicz, T.; Kozuchowska, S., and Vorbrodt, A.: Histochemical Examination of Damaged Cornea, Post. okul. 1:131-143, 1954.

29. Gemolotto, G.: Histochemical Investigation of the Mucopolysaccharides of the Cornea in Experimental Keratitis, Arch. ottal. 59:185-190, 1955.

30. Boyd, T.: Influence of Local Ascorbic Acid Concentration on Collagenous Tissue Healing in the Cornea, Brit. J. Ophth. 39:204-214, 1955.

31. Browning, C. W., and Lippas, J.: pHiso-Hex Keratitis, A. M. A. Arch. Ophth. 53:817-824, 1955.

32. Küchle, H. J.: The Action of Superficial Anesthetics on the Regeneration of Corneal Epithelium, Klin. Monatsbl. Augenh. 126:313-320, 1955.

33. Behrendt, T.: Experimental Study of Corneal Lesions Produced by Topical Anesthesia, Am. J. Ophth. 41:99-105 (Jan.) 1956.

34. Jaeger, W.: Corneal Damage by Vapor of Butyl Alcohol, von Graefes Arch. Ophth. 156: 480-483, 1955.

35. Miller, S.: Ocular Ocranosis (Hydroquinone): Its Properties and Uses, Tr. Ophth. Soc. U. Kingdom 74:349-366, 1954.

36. Popp, C.: Superficial Keratitis After External Drug Administration, Klin. Monatsbl. Augenh. 126:754-756, 1955.

37. Paton, R.: Keratoplasty, New York, McGraw-Hill Book Company, Inc., 1955.

38. Rycroft, B.: Corneal Grafts, London, Butterworth & Co., Ltd., 1955.

39. Laval, J., and Lloyd, R. I.: Successful Corneal Transplants in 4 Eyes of 2 Patients with Lattice Dystrophy, A. M. A. Arch. Ophth. 53:884-888, 1955.

40. Thomas, T.: Considerations Affecting Technique and Results in Keratoplasty, Tr. Ophth. Soc. U. Kingdom 75:473-515, 1955.

41. Croll, M., and Croll, L.: Corneal Transplantation (Technical Aspects of the Surgical Procedure), Eye, Ear, Nose, & Throat Month. 34: 375-387, 1955.

42. Spaeth, E.: Notes on Corneal Graft Surgery, Eye Digest 1:14-23, 1956.

43. Thomas, J. W. T.: Fixation of Corneal Grafts, A. M. A. Arch. Ophth. 54:1-5, 1955.

44. Abrahamson, I.; Brum, L., and Abrahamson, I., Sr.: A Simplified Technique for Corneal Transplantation, Am. J. Ophth. 41:79-85, 1956.

45. Alberth, B., and Szilagyi, I.: Fixing the Transplanted Human Cornea with Rabbit Cornea, Ophthalmologica 131:129-134, 1956.

46. Bock, J.: Previously Made Sutures for Partial Perforating Corneal Transplantation, Wien. klin. Wchnschr. 66:796-798, 1954.

47. Vejdovsky, V., and Mazanec, K.: Histological Examination of a Clear Corneal Graft After Keratoplasty, Ceskoslov. oftal. 11:208-213, 1955.

48. Speakman, J., and Jones, J.: Corneal Trephining for Penetrating Keratoplasty, Brit. J. Ophth. 40:216-221, 1956.

49. Votockova, J.: The Importance of Various Diameters of the Trephine in Corneal Transplantation, Ceskoslov. oftal. 11:234-241, 1955.

50. Sjogren, H.: Keratoplasty with Punch Forceps, Tr. Ophth. Soc. U. Kingdom 75:321-325, 1955.

51. Voisin, G., and Maurer, P.: Demonstration of the Role of Antibodies in the Rejection of Homografts, Transplant. Bull. 3:88-89, 1956.

52. Bollag, W.: Demonstration of Antibodies Following Homografts, Transplant. Bull. 3:43-44, 1956.

53. Hardin, C.: Common Antigenicity Between Skin Grafts and Total Lung Transplants, Transplant. Bull. 3:45-46, 1956.

54. Paton, R. T.: Immune Biological Response in Corneal Transplantation, Ann. New York Acad. Sc. 59:462-465, 1955.

55. Maumenee, A. E.: The Immune Concept: Its Relation to Corneal Homotransplantation, Ann. New York Acad. Sc. 59:453-461, 1955.

56. Klen, R.: Titre Changes of Group Antibodies in Keratoplasty, Ceskoslov. oftal. 11:129-135, 1955.

57. Bushmich, D.: The Incompatibility of the Tissues in Keratoplasty, Vestnik oftal. 34:24-28, 1955.

58. Babel, J.: Note sur la transplantation hétéroplastique intra-cornéenne de cornée et de sclérotique sur l'animal sensibilisé aux protéines hétérogènes, Ann. ocul. 188:22-26, 1955.

59. Michaelson, I. C., and Schrieber, H.: Influence of Low Voltage X-Radiation on Regression of Established Corneal Vessels, A. M. A. Arch. Ophth. 55:48-51, 1956.

60. Browning, C.: Evaluation of Beta Irradiation Therapy in Ophthalmology, South. M. J. 49: 298-303, 1956.

61. Michaelson, I. C.; Gluecker, L., and Stieglitz, E.: Influence of Low-Voltage X-Radiation on Inhibition and Prevention of New Vessels in Cornea: Comparison with Influence of Cortisone, A. M. A. Arch. Ophth. 52:77-84, 1954.

62. McDonald, J., and Wilder, H.: The Effect of Beta Radiation on Corneal Healing, Am. J. Ophth. 40:170-179 (Nov., Pt. 2) 1955.

63. Boudet, C.: Du Mode de vascularisation des greffons transfixiants sur leucomes post-inflammatoires, Arch. opht. 13:374-383, 1953.

64. Leigh, A.: Treatment of Gross Corneal Opacification by Lamellar and Annular Lamellar Keratoplasty, Brit. J. Ophth. 39:641-646, 1955.

65. Leigh, A.: Keratoplasty in Cases of Gross Corneal Opacification, Tr. Ophth. Soc. U. Kingdom 75:523-529, 1955.

66. Putchkowskaya, N.: Peripheral Lamellar Keratoplasty, Vestnik oftal. 34:11-16, 1956.

67. Stocker, F.: Management of Endothelial and Epithelial Corneal Dystrophy, Tr. Am. Acad. Ophth. 60:567-575, 1956.

68. Tillett, C.: Posterior Lamellar Keratoplasty, Am. J. Ophth. 41:530-533, 1956.

69. Rocha, H., and Coscarelli, E.: Lamellar Keratoplasty in Rodent Ulcer, Rev. brasil. oftal. 41:355-368, 1955.

70. Bonhoure, C.: Kératoplastie lamellaire par greffon conservé lyophilisé, Ann. ocul. 188:49-54, 1955.

71. Binder, H., and Binder, R.: Experiments of Plexiglass Corneal Implants, Am. J. Ophth. 41:793-797, 1956.

72. Kuwabara, Y.; Uyemura, Y., and Miyashita, T.: Experimental Keratoplasty with Use of

Acrylic Corneal Implant, Acta Soc. ophth. japon. 60:11-14, 1956.

73. Offret, G., and Chilaris, G.: Étude statistique des résultats de 170 greffes de cornée, Arch. opht. 15:373-382, 1955.

74. Zubczewski, A.: Results of 60 Transplantations of the Cornea, Polski tygodnik lek. 10:637-644, 1955.

75. Barkhash, S.: Partial Penetrating and Nearly Complete Corneal Transplantation in Children, Vestnik oftal. 34:16-24, 1955.

76. Paton, R.: Eye-Bank Program, Am. J. Ophth. 41:419-424, 1956.

77. Aguilar, M., and Del Rio Cabanas, J.: Conservation and Supply of Human Cadaver Corneas, Arch. Soc. oftal. hispano-am. 15:1075-1082, 1955.

78. McPherson, S.; Draheim, J.; Evans, V., and Earle, W.: The Viability of Fresh and Frozen Corneas, Am. J. Ophth. 41:513-519, 1956.

79. Illif, C.; Wood, R., and Hollander, D.: Successful Transplantation of a Frozen Human Cornea, Am. J. Ophth. 41:505-506, 1956.

80. McNair, J. N., and King, J. H., Jr.: Preservation of Cornea by Dehydration: A Preliminary Report, A. M. A. Arch. Ophth. 53:519-521, 1955.

81. Verrey, A.: Epidemic Keratoconjunctivitis, Ophthalmologica 129:261-270, 1955.

82. Hofmann, H.: Epidemic Keratoconjunctivitis in Styria 1952-1954, Klin. Monatsbl. Augenh. 127:438-465, 1955.

83. Cucco, G.: The Corneal Complications of Epidemic Keratoconjunctivitis, Rass. ital. ottal. 24:166-182, 1955.

84. Hoffmann, H., and Presinger, M.: Experimental Studies on the Virus of Keratoconjunctivitis Epidemica, Ztschr. Hyg. 141:180-196, 1955.

85. Schneider, J.; Kornsweig, A., and Feldstein, M.: Epidemic Keratoconjunctivitis, Am. J. Ophth. 42:266-269, 1956.

86. Sanders, M., and Alexander, R.: Epidemic Keratoconjunctivitis: Isolation and Identification of a Filterable Virus, J. Exper. Med. 77:71-96, 1943.

87. Cockburn, T. A.: The Present Status of Epidemic Keratoconjunctivitis, Am. J. Ophth. 38: 476-485, 1954.

88. Rowe, W. P.; Huebner, R. J.; Gilmore, L. K.; Parrott, R. H., and Ward, T. G.: Isolation of a Cytopathogenic Agent from Human Adenoids Undergoing Spontaneous Degeneration in Tissue Culture, Proc. Soc. Exper. Biol. & Med. 84:570-573, 1953.

89. Rowe, W. P.; Huebner, R. J.; Hartley, J. W.; Ward, T. G., and Parrott, R. H.: Studies of the Adenoidal Pharyngeal Conjunctival (APC), Group of Viruses, Am. J. Hyg. 61:197-218, 1955.

90. Fowle, A.; Cockeram, A., and Ormsby, H.: Virus Isolations from Patients with Keratoconjunctivitis, Am. J. Ophth. 40:180-188 (Nov., Pt. 2) 1955.

91. Fowle, A.; Simmons, V., and Ormsby, H. L.: A Study of Strains of APC Virus Isolated in Patients with Keratoconjunctivitis, Am. J. Ophth. 41:862 (May) 1956.

92. Ryan, R. W.; O'Rourke, J. F., and Iser, G.: Conjunctivitis in Adenoidal-Pharyngeal-Conjunctival Virus Infection: Pharyngoconjunctival Fever, A Newly Described Entity, A. M. A. Arch. Ophth. 54:211-216, 1955.

93. Doane, F.; Rhodes, A. J., and Ormsby, H. L.: Experiences with APC Infections in the Summer of 1955, Am. J. Ophth. 41:693, 1956.

94. Sage, H. M., Jr., and Suie, T.: Adenoidal-Pharyngeal-Conjunctival Virus Infection with Associated Corneal Involvement, A. M. A. Arch. Ophth. 55:269-270, 1956.

95. Ormsby, H.: An Interim Report on Ocular Diseases Due to APC Viruses in Ontario, Canad. J. Pub. Health 46:500-505, 1955.

96. Jawetz, E.; Kimura, S.; Hanna, L.; Coleman, V.; Tygeson, P., and Nicholas, A.: Studies of the Etiology of Epidemic Keratoconjunctivitis, Am. J. Ophth. 40:200-209 (Nov., Pt. 2) 1955.

97. Balducci, D.; Zaiman, E., and Tyrrell, D.: Laboratory Studies of APC and Influenza C Viruses, Brit. J. Exper. Path. 37:205-218, 1956.

98. Hall, R. L.; MacKneson, R. G., and Ormsby, H. L.: Studies of Immunity in Experimental Herpetic Keratitis in Rabbits, Am. J. Ophth. 39:226-233 (Feb., Pt. 2) 1955.

99. Speakman, J., and Ormsby, H.: Studies of Immunity in Vaccinia Keratitis in Rabbits, Am. J. Ophth. 40:194-199 (Nov., Pt. 2) 1955.

100. Cucco, G.: Subepithelial Keratitis (Clinical Significance and Various Morphological Aspects), Arch. ottal. 59:317-322, 1955.

101. Peterhans, A.: A Statistical Study of 426 Cases of Herpes Cornea, Ophthalmologica 130: 244-271, 1955.

102. Simkova, M.: Changes of Corneal Innervation in Herpetic Keratitis, Ceskoslov. oftal. 11:138-143, 1955.

103. Weekers, L.: Le Rôle des virus endormis dans la pathogénie de certaines keratitis, Arch. opht. 15:839-845, 1955.

104. Wolter, J., and Shapiro, I.; and Whitehouse, F.: Pathology of Experimental Primary Herpetic Keratitis, Am. J. Ophth. 41:639-645, 1956.

105. Selye, H.: Prevention of Cortisone Overdosage Effects with the Somatotrophic Hormone (STH), Am. J. Physiol. 171:381-384, 1952.

106. Griswold, C., and Bowen, S.: Inactivated Influenza Virus Vaccine in Therapy of Herpes Zoster: Clinical Evaluation, Texas J. Med. 49:693-695, 1953.

107. Hallett, J. W.; Naib, K., and Leopold, I. H.: Control of Experimental Herpes Simplex

Virus Keratitis: Hormonal, Vaccine, and Antibiotic Therapy, A. M. A. Arch. Ophth. 54:573-579 (Oct.) 1955.

108. Vannini, A., and Pettinati, S.: Plesiotherapy in Herpetic Affections of the Cornea, Rass. ital. ottal. 24:391-399, 1955.

109. Graham, J., and Leskowitz, S.: Enhanced Production of Antibodies by Local Irradiation, J. Immunol. 76:110-111, 1956.

110. Graham, J.; Graham, R.; Neri, L., and Wright, K.: Enhanced Production of Antibodies by Local Irradiation: I. Measurement of Circulating Antibodies, J. Immunol. 76:103-109, 1956.

111. Doane, F.; Rhoades, A., and Ormsby, H.: Tissue Culture Techniques, Am. J. Ophth. 40:189-193 (Nov., Pt. 2) 1955.

112. Ley, A. P., and Sanders, T. E.: Fungus Keratitis: A Report of 3 Cases, A. M. A. Arch. Ophth. 56:257-264, 1956.

113. Mitsui, Y., and Hanabusa, J.: Corneal Infections After Cortisone Therapy, Brit. J. Ophth. 39:244-250, 1955.

114. Shinichi, H., and Potts, A.: The Penetration of Cortisone and Hydrocortone in Ocular Tissues, Am. J. Ophth. 40:211-215 (Nov., Pt. 2) 1955.

115. Niedermeier, S.: Local Cortisone and Hydrocortisone Therapy, Klin. Monatsbl. Augenh. 126:337-339, 1955.

116. Gandolfi, A., and Montaldi, M.: The Possibility of Eliminating the Antiepithelializing Effect of Hydrocortisone by Means of Combination with Chlorophyll, Arch. ottal. 59:5-12, 1955.

117. Pentini, G., and Sforzolini, G.: Hydrocortisone and Repair of Experimental Corneal Wounds in Rabbits, Gior. ital. oftal. 8:374-382, 1955.

118. Palmerton, E.: The Effect of Local Cortisone on Wound Healing in Rabbit Corneas, Am. J. Ophth. 40:344-353, 1955.

119. Eadie, S., and Thompson, M.: Keratoconjunctivitis Sicca Treated with Cortisone and ACTH, Brit. J. Ophth. 39:90-97, 1955.

120. King, J. H., and Weimer, J. R.: Prednisone (Meticorten) and Prednisolone (Meticortelone) in Ophthalmology: Experimental and Clinical Studies, A. M. A. Arch. Ophth. 54:46-54, 1955.

121. King, J.; Passmore, J.; Skeehan, R., and Weimer, J.: Prednisone and Prednisolone in Ophthalmology, Tr. Am. Acad. Ophth. 59:759-770, 1955.

122. Hogan, M.; Thygeson, P., and Kimura, S.: Effects of Prednisone and Prednisolone in Ocular inflammation, Tr. Am. Acad. Ophth. 59:779-782, 1955.

123. Proptopopov, S., and Galchin, S.: The Use of Ethylcellosolf in the Treatment of Trachoma, Vestnik oftal. 1:34-36, 1956.

124. Breinin, G. M., and DeVoe, A. G.: Chelation of Calcium with Edathamil Calcium-Disodium in Band Keratopathy and Corneal Calcium Affections, A. M. A. Arch. Ophth. 52:846-851, 1954.

125. Konig, H., and Marty, F.: A New Solvent for Calcareous Deposits on the Cornea, Ophthalmologica 129:219-224, 1955.

126. Katavisto, M.: Streptokinase-Streptodornase in the Treatment of Ulcus Serpens Corneae, Acta ophth. 34:214-217, 1956.

127. Ambrosio, A.: The Repair of Corneal Wounds with Lyophilized Erythrocytes, Arch. ottal. 59:333-343, 1955.

128. Kamiya, S.: Mass Treatment of Trachoma, Am. J. Ophth. 42:269-283, 1956.

129. Agarwal, L.; Saxena, R., and Gupta, B.: Treatment of Trachoma, Am. J. Ophth. 40:553-556, 1955.

130. Agarwal, L., and Malik, S.: Tetracycline in Trachoma, Brit. J. Ophth. 39:759-761, 1955.

131. Petrohelos, M. A., and Wolter, J. R.: Necroscleritis Nodosa: Clinicopathologic Report of a Case, A. M. A. Arch. Ophth. 55:221-228, 1956.

132. Renard, G.; Lievre, J.; Bloch, M., and Saraux, H.: Scléromalacies et scleromalacies perforantes, Arch. opht. 15:479-486, 1955.

133. Ostriker, P. J.; Ostriker, M., and Laskey, M. A.: Keratitis and Scleritis Associated with Felty's Syndrome, A. M. A. Arch. Ophth. 54:858-862, 1955.

Correspondence

LUNEBURG THEORY OF VISUAL GEODESICS IN BINOCULAR SPACE PERCEPTION

To the Editor:—The recent article by Paul Squires (A. M. A. ARCH. OPHTH. 56:288-297, 1956) is, we believe, of some interest, but certain points do need clarification.

The Luneburg theory was developed to describe only certain aspects of binocular visual experience, those associated with the purely geometric properties of size and location of objects. The use of small point sources of light in an otherwise totally dark room is an experimental design appropriate to the Luneburg theory. Though Squires' use of small black dots in a diffusely illuminated room could certainly represent an important experiment in its own right, it is not an experimental design appropriate to the Luneburg theory. In this instance, extraneous visual clues are introduced which the theory does not attempt to account for—among other things, color and brightness of objects and, especially, the configuration of the room itself. Such a configuration, possessing rich monocular perspective clues, has been explored, by the complete sensory armamentarium, many times in the past, so that judgments relating to it cannot really be said to be exclusively, or even predominantly, binocular. The mathematics of the visual space under such conditions may be, and, indeed, is most probably, entirely different from that describing the restricted visual space of the Luneburg geometry. It is not permissible to claim that, because a fairly adequate description of visual light does not also describe x-rays equally as well, the description of light rays is, therefore, in itself, incorrect. That alleys under conditions of ambient illumination are different from darkroom alleys is an interesting point, though we might have suspected it. But the very fact of this difference tells us nothing whatsoever about the adequacy, or the inadequacy, of the description of the alleys under either condition by itself.

The point is of particular relevance to Squires because he concludes that the two experimental designs do, in fact, give the same results. This would indeed be an important addendum, but to base it on only two observations (one of P. C. S. in the dark and one of T. S. under diffuse illumination) is perhaps not the most conservative approach. In any case, Squires probably did not really intend this finding as a "contradiction"—his wording is perhaps misleading.

This is also true of his use of the word "photopic." All alley experiments so far completed have been photopic. To imply, by contrast with his own studies, that some alleys were done under scotopic conditions is not correct. "Darkroom" alleys are most definitely also photopic alleys. In fact, it is more than likely that truly scotopic (i. e., rod vision) alleys cannot be measured at all, because of the markedly reduced peripheral acuity and the increased tendency towards autokinesis.

Second, to evoke experimental findings wherein the observer's attitude can shift the results one way or another is either to invalidate the experimental procedure itself or to disqualify oneself as an observer. Thus, whatever is the "depth-perceiving attitude" that certain observers seem to adopt, it can only contaminate the results. Moreover, it violates, most directly, the basic and fundamental definition of the distance alleys.

Squires misses the fact that the distance alleys are not to be "visual alleys" at all. He appears to have been mislead by the terminology. The only point at issue in the distance alleys is that the widths of the alleys should be visual geodesics, normal to the median symmetrical line of sight. In the usual experiment on the distance alley, only four points of light appear, the two fixed far-points, and the two variable points placed somewhat nearer. In this case, the observer constructs only two equally-sized black spaces (the apparent frontal spaces between the two pairs of lights). The concept "alley" never once enters in. It is true, of course, that we eventually fit a mathematical curve through the points, to make them into

a "mathematical alley"; but never into a "visual alley." Luneburg adopted the term from Blumenfeld, and it has unfortunately persisted.

While it is true that Luneburg's choice of the hyperbolic metric was based primarily upon his interpretation of the alley experiments, it is simply false to state that "Luneburg developed his equations principally upon the basis of the Blumenfeld alleys." Suppose, for example, that we had experimental results which clearly showed that visual space was not a hyperbolic space; the question would still exist as to whether visual space was a Riemannian space. A major part of the Luneburg theory pertains to this more general question and would be retained independently of the alley-experiments.

Indeed, Luneburg did anticipate that much of his work was of the nature of a tentative hypothesis and that it might need reformulation in the light of future experimentation. Moreover, as the experiments now stand, we can have no predilection for choosing, necessarily, a hyperbolic space, or even a Riemannian space. Further clarification of these questions awaits extremely careful experiments. In the meantime, the Luneburg theory does indicate the direction in which such experimentation may move and provides a framework which future work in this region cannot ignore.

In summary, we wish to emphasize that the highly technical nature of the problems inherent in the development of a geometry of binocular visual space, and the active experimental work in progress, make necessary very critical examination of all contributions in this field.

THORNE SHIPLEY, PH.D.
GORDON L. WALKER, Ph.D.
American Optical Company
Research Center
Southbridge, Mass.

To the Editor:—Replying to Drs. Shipley and Walker, I wish briefly to say:

1. ***Shipley and Walker*** claim that work done in the darkroom alleys cannot be said to have been carried out under scotopic conditions.

Reply: Unquestionably, points of light in a darkroom are perceived by the foveal cones, but a few points of light in a wholly dark surround do not prevent scotopic adaptation (the stars are seen at night with dark-adapted eyes). Therefore, experiments with darkroom alleys involve foveal (cone) perception by eyes which are in a state of scotopic adaptation—a complex which has not been sufficiently examined by darkroom experimenters. However, I have no objection to using the term darkroom alleys and have in general used this term in my article.

2. ***Shipley and Walker*** claim I conclude that the white lighted and darkroom alleys give the same results.

Reply: Nowhere do I conclude that the same results were obtained from white lighted and darkroom alleys. All I claimed was "The algebraic sign of the non-Euclidean metric is not affected, so far as our data reveal, and under the values of θ used, by the differences between white lighted and darkroom conditions" (p. 296). "Algebraic sign" and "results" are not synonomous expressions.

3. ***Shipley and Walker:*** "In any case, Squires probably did not really intend this finding as a 'contradiction'—his wording is perhaps misleading."

Reply: Here, Shipley and Walker refer to the matter dealt with under 2 above. I cannot find where I used the word "contradiction" in this connection.

4. ***Shipley and Walker:*** "This would indeed be an important addendum, but to base it on only two observations (one of P. C. S. in the dark and one of T. S. under diffuse illumination) is perhaps not the most conservative approach."

Reply: These two "observations" suffice to establish a prima facie case, at any rate. We note that Shipley and Walker recognize the importance of this line of attack, even though it is historically true that the Luneburg theory was based on clueless binocular vision in a darkroom. The "two observations" referred to by Shipley and Walker consisted of one morning spent by Shipley in setting up the white lighted alleys and two afternoons spent by me in Shipley's darkroom.

5. ***Shipley and Walker:*** ". . . it is simply false to state that 'Luneburg developed his equations principally upon the basis of the Blumenfeld alleys'."

Reply: Luneburg states, "The alley experiments thus give us the possibility of deciding by experiment which metric is characteristic for our spatial sensations. Blumenfeld's data show clearly that the distance curves lie outside the parallel curves. Thus if we are allowed to identify his parallel alleys with the above-discussed alleys, we must conclude that the psychometric of space sensations is hyperbolic" (R. K. Luneburg: Mathematical Analysis of Binocular Vision, Princeton, N. J., Princeton University Press, 1947, p. 80).

L. H. Hardy et al. state, "The most striking evidence that visual space is non-euclidean lies in the distinction in visual perception between apparently parallel straight lines and curves of apparent equidistance" (Hardy, L. H.; Rand, G.; Rittler, M. C.; Blank, A. A., and Boeder, P.: The Geometry of Binocular Space Perception, Elizabeth, N. J., J. Schiller, 1953, p. 20.

6. *Shipley and Walker:* ". . . to evoke experimental findings wherein the observer's attitude can shift the results one way or another is either to invalidate the experimental procedure itself or to disqualify oneself as an observer."

Reply: Shipley and Walker here present a spurious dilemma, scarcely worthy of a reply. *Einstellung* (adjustment, attitude, set) and *Anlage* (predisposition) are integral to all observations and mental processes whatsoever. The observer imposes pattern upon aggregates of stimuli. The duty laid upon the experimenter with respect to set or attitude is to control it in so far as possible. Reading of my instructions to the observers will show that I made every effort to get them "to view the" parallel "alley . . . as a *whole*" and to make the judgments on apparent widths for the distance alley *"while holding your depth-perception attitude"* (p. 291).

7. *Shipley and Walker:* "Such a configuration, possessing rich monocular perspective clues . . ."

Reply: My instruction to observers was: "You must use *both* eyes at all times . . ." (p. 291). This instruction was a critical one: I emphasized and re-emphasized it during the experimental sittings. As a matter of fact, I insisted that binocular viewing be carried out at all times while constructing both the parallel and equidistance alleys. I have no reason to believe that any observer violated this cardinal instruction.

8. *Shipley and Walker:* "In this instance, extraneous visual clues are introduced . . . especially, the configuration of the room itself."

Reply: Certainly visual clues (secondary criteria) are afforded by the white lighted condition, as contrasted with the clueless darkroom situation. But man does not ordinarily carry on a mole-like existence. I have been interested in discovering whether, for binocular vision under white light, observers show a difference in the algebraic sign of the Riemannian curvature under white lighted and darkroom conditions. As stated in my reply, 2, above, I have not found difference in algebraic sign of K, for the values of θ used, under the two conditions of illumination.

Renshaw has well said: "But of course the question arises: how much does one artificialize the situation by elimination of normal field or peripheral seeing conditions? The point is debatable." He also states: "The question of the proper metric for binocular space remains open" (cited by me, p. 295).

9. *Shipley and Walker:* "Squires misses the fact that the distance alleys are not to be 'visual alleys' at all."

Reply: It should hardly be necessary for me to remark that I have been fully aware at all times that, historically, the equidistance alleys have not been treated as "visual alleys." And this is exactly the crucial objection I have interposed with respect to the Luneburg theory: that the Blumenfeld distance alley data used by Luneburg were not data derived from a "visual" alley.

Comments: It may very well be that in searching for *the* Riemannian metric of binocular space we are pursuing a fata morgana. We more than suspect that the final solution—if there be such—will not be in terms of a single metric, even for one observer, but in terms of *metrics.*

Among the many highly intricate and obscure problems to be solved in connection with the Riemannian curvature of binocular space is the role enacted by *die eidetische Anlage* (eidetic disposition) in determining the sense of curvature (geometric) of the apparent frontoparallel plane at various distances. The investigations of Krönçke, vom Hofe, E. R. Jaensch, and Reich indicate how important this eidetic disposition may be for determination of the binocular space metrics (references to these investigations may be found in Ogle, K. N.: Researches in Binocular Vision, Philadelphia, W. B. Saunders Company, 1950; see p. 23).

PAUL C. SQUIRES, Ph.D.
Human Engineering Branch
Medical Research Laboratory
U. S. Naval Submarine Base
New London, Conn.

Society Transactions

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

I. S. Tassman, M.D., Chairman
William E. Krewson, 3rd, M.D., Clerk
March 15, 1956

Keratotomy in Mooren's Ulcer of The Cornea. R. D. HARLEY, M.D. (by invitation).

Mooren's ulcer is a relatively rare disease. In the available literature it was unusual for one ophthalmologist to have reported more than three cases of his own even after working for many years.

In over 25% of cases it is bilateral, but several years may elapse between involvement of each eye. It characteristically occurs in elderly people, but case reports include all ages.

The disease begins with a gray patch of infiltration at the corneal margins approximately 1 mm. from the limbus. The ulcer spreads slowly along the margin and gradually in toward the center of the cornea. After the ulcer has been present for two weeks or longer, a dehiscence or furrow becomes apparent with its base on the corneal side, along with an overhanging margin. The ulcer penetrates about half way through the cornea and never appears to go deeper. Perforation is rare unless secondary infection is present. Healing takes place very slowly from the periphery, with the development of new vessels and scar tissue. In front of the advancing border there is a gray infiltration, and beyond this point the cornea remains completely clear.

Symptoms of pain and photophobia are very severe in spite of the mild tissue response to inflammation. The pain is not controlled by the use of local anesthetics. In addition to the local eye discomfort, the pain seems to involve most of the area supplied by the first division of the fifth nerve. Even heavy sedation may give but temporary relief, and the increasing exhaustion of the patient becomes as much of a problem as the eye. Unfortunately, in too many cases, despite all available treatment, the pain and ulcer continue unabated and the prognosis for future vision becomes poor.

A case involving both eyes was presented which was successfully treated by delimiting keratotomy after a conjunctival flap failed to help. Penetrating keratotomy incisions from 11 to 7 o'clock and 7 to 4 o'clock were required for the left eye, but quadrilateral keratotomies were required for the right eye.

Involvement of the second eye took place 18 months after the attack in the first eye. The visual acuity has remained at 20/30 in the right eye and 20/70 in the left eye for the past three years, and there has been no sign of recurrence.

The production of hypotony over a period of time seems to offer good results. This can be accomplished by delimiting keratotomy, repeated paracenteses or making a fistulous track with a cautery. A ring-shaped lamellar corneal graft has received good reports and may be used prior to a keratotomy.

Discussion

DR. GLEN G. GIBSON: Dr. Harley should be congratulated for his heroic efforts and his gratifying end-result, which he has achieved in a condition that

all too frequently terminates in blindness or in enucleation. He was kind enough to permit me to see this patient, and I wish to confirm his diagnosis. His description does not adequately portray the hopeless appearance of these eyes and the intractable nature of Mooren's ulcer, of which his patient is a classical example in every detail. He has stated that the basic abnormality and pathogenesis of Mooren's ulcer is unknown. The clinical course, the response to therapy, and the way in which repair was accomplished would tend to suggest that diminished nutritive supply, secondary to vascular sclerosis, played an important role in the pathogenesis of this process. Such a simple explanation does not suffice, however, owing to the common occurrence of the advanced stage of vascular sclerosis and the infrequent incidence of Mooren's ulcer. The delimiting keratotomy is admittedly an empirical procedure, and the benefits from this operation can presumably be attributed to two main and different mechanisms. First, the delimiting keratotomy has a confining influence on the necrotic process in corneal disease, which at times spreads by the necrotizing effect of the necrotic tissues on the adjacent vital cells by direct continuity. A delimiting keratotomy tends to prevent this type of extension, and that is one mechanism by which benefits were probably derived.

The other beneficial effects are related to hypotony. Presumably a number of alterations occur following prolonged hypotony. These alterations are not easy to measure, but it can be postulated that increased secretory activity by the ciliary processes, leading to a plasmoid aqueous, accounts for some of the beneficial effects. Dilatation and migration of vascular loops of superficial limbal plexus occurs. This is essential to repair in this process. Likewise, there is a reduction in tissue tension, which has a beneficial effect on the transfer of intracorneal fluid. There is increased permeability of the cornea, owing to the obvious discontinuity of the epithelium and endothelium. The keratotomy may accelerate the elimination of the toxic material from the necrotic ulcer.

The use of chemical cautery and diathermy is said to be beneficial in the treatment of this condition, but it should be done with a clear-cut concept of the difference in the therapeutic objective in pryogenic ulcer and in Mooren's ulcer. In cases of purulent corneal ulcer diathermic fulguration is the method of choice. It should be the principal method for eradication of the infection, and antibiotics should be reserved for a secondary role in most cases. The objective is not only to destroy the necrotic tissue but to extend beyond the visual limits of the lesion to destroy the organisms, which presumably are located beyond the visible margins of lesions. To be successful diathermic fulguration should be done in a somewhat radical manner. In contrast to this, in Mooren's ulcer the objective is merely to destroy necrotic tissue, and not to eradicate infection. The fulguration with diathermy should be done in a highly conservative manner, because here we are employing a very devitalizing agent in a tissue which is already devitalized. I should like to emphasize a point which Dr. Harley passed over rather lightly, and that is the fact that part of his success was due to the fact that he closely adhered to one of the basic principles in corneal therapy. He kept the eye thoroughly atropinized. The incomplete or inadequate utilization of atropine constitutes one of the greatest therapeutic errors in present-day ulcer therapy.

Finally, I think that we can all approach our next case of Mooren's ulcer with a sense of diminished futility after hearing Dr. Harley's interesting case report.

DR. JAMES S. SHIPMAN: I should like to compliment Dr. Harley on his beautiful result. My own experience with this operation in other types of malignant ulcers has been very satisfactory. I do not think this procedure has been done or is being done as much as it should be. We used to refer to this operation, and I still refer to it, as a Saemisch section; I think I must have done at least four or five, and I have been present when another five or six have been done. This operation was first called to my attention by Dr. B. F. Baer about twenty-five years ago. I will never forget the first one I saw him do, how brutal it looked, and how I never could feel that the patient would ever see again. But, gentlemen, it does work, especially when it is done soon enough. I think Dr. Harley is to be congratulated that he had nerve enough to try this procedure in a case of Mooren's ulcer and to do it as it should be done. Certainly, it proved to be perfect for this case, and it did stop the progress of the condition. I have seen it work in other cases and save eyes that would otherwise have been lost, but not always saving so much vision as he did here.

The Electroretinogram in Man During Blackout. T. D. DUANE, M.D. (by invitation).

Electroretinograms from five subjects were recorded on the human centrifuge under varying degrees of accelerative stress up to and including blackout and unconsciousness. These findings were correlated with changes in the retinal circulation and with the consensual light reflex. It was found that the electroretinogram could not be employed as an objective measurement of blackout, since it persisted throughout all the experiments, as did the consensual light reflex. These findings indicate a likely origin of blackout in or near the ganglion-cell layer of the retina.

Discussion

DR. FRANCIS H. ADLER: Dr. Duane, we are all fascinated by your work and the amount of torture that you have put yourself through in this experimentation concerning the possible site of blackout. I cannot see from your diagram how pupillary impulses get through, while visual impulses are blocked, unless you postulate separate optic nerve fibers for these functions.

I wonder if it would be helpful to perform another experiment, and that would be to record under these conditions an electroencephalogram with the ordinary alpha rhythm and see whether you can still get "driving" through. The alpha rhythm can be influenced with intermittent illumination from the retina. In other words, if you expose an eye to flicker, you can under normal conditions show the influence of flicker on the rate of the cortical impulses. That is called driving the alpha rhythm.

Now I would like to know whether under conditions of blackout you can demonstrate "driving." If you cannot, it means impulses are not reaching the cortex, and that would mean that blackout is solely in the retina. If you can still get driving, it would mean that blackout may be partially in the retina and partially in the cortex.

DR. T. D. DUANE: In the first place, I should like to thank Dr. Adler for his comments. When you say that you are not quite certain as to our scheme—is that because of a poor diagram or because you do not believe it to be physiologically possible?

DR. FRANCIS H. ADLER: Well, let us assume that the ganglion cell is the last point at which blackout could effect the retinal conduction unless you are going to

assume it is on the nerve fiber. Let us take the ganglion cell. Now, if it is anywhere between the ganglion cell and the receptors, why would not it block the pupillomotor fiber as well as the visual?

DR. T. D. DUANE: First let me state we think that the synapse is more susceptible to anoxia than the ganglion cell itself.

Now there are several synapses in there between the photoreceptor and ganglion cell. We have pinpointed to this particular synapse because we think that the other synapse between the photoreceptor and the pupillomotor afferent tract is deeper in the retina, more in the deep bipolar region, or closer to the photoreceptor itself. This receives a certain supply of oxygen, and so forth, from the deeper portion of the retina, also from the choroid. Now the ganglion cell and the ganglion synapses lie within the outer bipolar area; it does not get anything, or very little, from the deeper source of the supply for the retina—I mean that closer to the photoreceptor cell. So we conclude that when reflex action occurs under these conditions of blackout that photoactive and relatively insensitive nerve fibers continue to function. We think that in the visual pathway the photoreceptor and bipolar areas function but the impulse is blocked at the region of synapse between the ganglion cell and bipolar area, where the blood supply has been cut off, as we observed.

Anyway, that is the theory. You see it seems there are not the same number of synapses and pathways for pupillary as there are for visual fibers.

DR. FRANCIS H. ADLER: That is the assumption that you accept. In other words, all the evidence points to their being the same.

DR. T. D. DUANE: And that is not what you say in your book.

DR. FRANCIS H. ADLER: The Bible says, "Would that mine enemy would write a book." The evidence is certainly not conclusive that they are separate. Many have tried to make them separate because of so many clinical facts which suggest it.

DR. T. D. DUANE: You are right. As I say, the tendency is for the physiological basis to help support the anatomical. I do not think there is too good evidence for them either, but the second part of your comment is very interesting about the photic driving.

Dr. Lewis and I, before he left, had proposed experiments in which we had planned to do this very thing. Both under room condition, i.e., pressure on the globe, plus during blackout on the centrifuge. However, Dr. Lewis is now measuring intravascular phenomena and so I do not know if we will get to it or not.

I. S. TASSMAN, M.D., Chairman
WILLIAM E. KREWSON 3rd, M.D., Clerk
April 19, 1956

The Toxic Amblyopias: A Reevaluation. ALBERT M. POTTS, M.D. (by invitation).

The concept of "toxic amblyopia" is essentially a residual one which has remained after subtracting diseases with ophthalmoscopic findings from the ancient concept of "gutta serena." It therefore causes the lumping together of entities with many different biochemical mechanisms and different local sites of action. This causes unnecessarily muddled thinking in a medical science where the tools are available to work out specific biochemical mechanisms of disease.

Three examples considered in some detail serve to illustrate the disadvantages of the concept of toxic amblyopia.

One of these is the case of methyl alcohol poisoning, which has been under study for some years in the Western Reserve Laboratory. Because of the difficulties in controlling variables in human poisoning cases, animal experimentation was resorted to. It was soon found that methyl alcohol poisoning in lower animals was simply organic solvent narcosis and bore little relationship to the human disease. In rhesus monkeys, however, the human disease picture was faithfully reproduced and on analysis proved to be three concentric diseases which could be demonstrated separately with proper technique. Disease I was the organic solvent narcosis seen in any animal with doses of 10 gm/kg. of methyl alcohol and was similar to poisoning with comparable doses of ethyl alcohol. Disease II was seen in monkeys with lower doses of methyl alcohol and was characterized by a latent period of approximately 20 hours followed by the onset of acidosis and death. If acidosis was combatted by administration of base, Disease III was seen. This is central nervous system involvement independent of acidosis and specifically is manifested by severe retinal edema and optic neuritis and by necrosis of the basal ganglia, and sometimes late death.

Thus, in the case of methyl alcohol poisoning one is dealing with an unsuspectedly complex entity which is not in the least devoid of ophthalmoscopic findings and thus is really not an amblyopia at all.

The second example is the so-called tobacco-alcohol amblyopia. To understand its creation and persistence in the face of so many logical arguments against it, one must appreciate the high moral note at its inception and should recall its companion, Burns' amaurosis, which inexplicably fell by the wayside much earlier. In the light of modern work—the statistical study by Usher and the nutritional investigations of Carroll—it is evident that tobacco-alcohol amblyopia is not toxic at all but is a deficiency disease and is related to tobacco and alcohol only through their anorexic effect.

The third example is that of mescaline intoxication, which by definition may certainly be called a toxic amblyopia. However, if we do so we lump the diseases due to retinal involvement, such as methyl alcohol poisoning, with those that affect the occipital cortex—a piece of irrationality that has neither anatomical nor biochemical logic to defend it.

For these reasons it may be that the concept of "toxic amblyopia" which served us well in the days of descriptive medicine is proving a logical encumbrance in this day of biochemical and biophysical mechanism and should be given an honored resting place.

News and Comment

ANNOUNCEMENTS

National Medical Foundation for Eye Care.—The National Medical Foundation for Eye Care, a nonprofit scientific and educational institution, incorporated in New Jersey, has been organized by ophthalmologists of the country to provide American ophthalmology with an agency to present to the public generally and to fellow physicians pertinent information on the care and treatment of the eyes.

Dr. Ralph O. Rychener, of Memphis, is president of the Foundation; Dr. Edwin Forbes Tait, of Norristown, Pa., vice-president, and Dr. Charles E. Jaeckle, of East Orange, N. J., secretary-treasurer.

Members of the Board of Trustees, in addition to the above-named, are Drs. Alson E. Braley, Iowa City; Frederick C. Cordes, San Francisco; Paul Chandler, Boston; J. Spencer Dryden, Washington, D. C.; Harold F. Falls, Ann Arbor, Mich.; Everett L. Goar, Houston, Texas; Erling W. Hansen, Minneapolis; A. D. Ruedemann, Detroit; Barnet R. Sakler, Cincinnati, and Derrick Vail, Chicago.

Applications are available through Dr. Charles E. Jaeckle, Secretary-treasurer, at 136 Evergreen Place, East Orange, N. J. The Foundation will establish an administrative office in New York City about Jan. 1, 1957, and will also make available an Affiliate Membership for persons other than doctors of medicine who are interested in aiding the purposes of the Foundation, Dr. Rychener announced.

The object and purpose of the Foundation is to advance the public welfare by (1) gathering, receiving, assembling, and studying information relative to eye care; (2) fostering and/or engaging in investigations and research in all aspects of eye care; (3) sponsoring studies of educational, socio-economic, and scientific factors affecting eye care; (4) issuing reports and otherwise disseminating information relative to eye care to the general public and to members of the medical profession and ancillary workers; (5) promoting the conservation of vision and the prevention of blindness through the wider dissemination of knowledge of the eye—its defects, its disfunctions, and its other diseases and their relation to general health; (6) promoting a more effective utilization of the scientific knowledge of ophthalmology and the other related branches of medicine; (7) generally performing any act, related to the foregoing, designed to present to the public generally and to the medical profession all pertinent information on the care and treatment of the eyes.

Ophthalmological Society of the United Kingdom.—The Annual Congress of the Ophthalmological Society of the United Kingdom will be held at the Royal Society of Medicine, 1 Wimpole St., London, W. 1, on April 11-13, 1957.

The Presidential Address will be delivered by Mr. J. J. Healy, on "The Intraocular Circulation in Arterio-Sclerosis and High Blood Pressure."

The subject for dscussion will be "Ocular Aspects of Diabetes." This will be opened by Prof. G. I. Scott, Dr. Norman Ashton, and Dr. J. D. N. Nabarro. Members who wish to take part in the subsequent discussion are advised to intimate their intention before the opening of the Congress. It is emphasized that no member may speak for more than ten minutes.

There will also be a short symposium on "Congenital Cataract."

On this occasion the Bowman Lecture will be delivered by Sir Stewart Duke-Elder, his subject being "The Aetiology of Glaucoma."

Members wishing to read a short paper or to give a short pictorial demonstration are asked to send the title, together with an abstract, to Mr. J. R. Hudson, not later than Nov. 30, 1956. Those wishing to show films should also communicate with Mr. Hudson by the same date.

The annual dinner will be held at the Trocadero Restaurant on Thursday, April 11. Members may bring guests. A Trade Exhibition will be held in the Cowdray Hall (next door to the Royal Society of Medicine).

On account of the difficulty in obtaining hotel accommodations in London, all members who will require it are advised to make their arrangements in good time.

Association for Research in Ophthalmology.—The annual meeting of the Western Division of the Association for Research in Ophthalmology will be held at Stanford University Medical School, 2340 Clay St., San Francisco, on Monday, Jan. 28, and Tuesday, Jan. 29, 1957.

National Committee for Research in Ophthalmology and Blindness.—A National Committee for Research in Ophthalmology and Blindness was recently formed by representatives from the four national ophthalmic societies. Members of the committee are Bernard Becker, Washington University, and A. Edward Maumenee, Johns Hopkins University, representing the American Academy of Ophthalmology and Otolaryngology; Michael J. Hogan, of the University of California, and Albert D. Ruedemann Sr., Wayne University, representing the American Medical Association, Section on Ophthalmology; Alson E. Braley, University of Iowa, and David G. Cogan, Harvard University, representing the American Ophthalmological Society; and Irving H. Leopold, University of Pennsylvania, and Frank W. Newell, University of Chicago, representing the Association for Research in Ophthalmology.

The committee plans to stimulate increased interest in ophthalmic research and to cooperate with and act as an advisory group to all persons and agencies interested in blindness, the prevention of blindness, vision, and research in the basic disciplines of ophthalmology.

Annual Clinical Conference of Wills Eye Hospital.—The Ninth Annual Clinical Conference of the Staff and Society of Ex-Residents of Wills Eye Hospital will be held at the hospital on Feb. 8 and 9, 1957. The Conference this year will be of especial interest, since it will be an important feature in commemorating the 125th anniversary of the founding of the hospital.

The Bedell Lecture will be delivered by Dr. John M. McLean, of New York, on the subject of "Management of the Primary Glaucomas."

The program will also include scientific papers by members of the staff and ex-residents of the hospital, technical exhibits, and a color television program sponsored by Smith, Kline & French Laboratories which will present ocular surgery, case presentations, and demonstrations of procedures and techniques.

On Friday evening, Feb. 8, there will be an informal reception and supper for the ophthalmologists and their wives. On completion of the two-day program, the Wills Eye Hospital Society will hold its annual meeting and dinner at the Union League, Philadelphia, on Saturday, Feb. 9, 1957, at 6:30 p. m.

Prior to the conference there also will be a meeting, preceded by dinner, of the Ophthalmological Section of the College of Physicians in Philadelphia, on Thursday evening, Feb. 7, 1957, at which Dr. James H. Allen, of New Orleans, will be the guest speaker. All ophthalmologists are invited.

Pan-American Association of Ophthalmology.—The Pan-American Association of Ophthalmology has selected Caracas, Venezuela, as the meeting place for the Sixth Pan-American Congress, Jan. 31 through Feb. 7, 1960. Secretary General is Dr. R. Hernandez Miliani; President, Dr. Jesus Rhode, Caracas.

Books

Cataract Surgery—Its Evolution and Practice. By Nabin Kishore Bidyadhar. Price, not given. Pp. 324, with 33 illustrations. Srimati Rameshanandini Devi, Sonpur Raj, Orissa, India, 1955.

Books on cataract surgery are always of interest to the ophthalmologist. This book by the eminent Indian ophthalmologist describes the evolution of cataract surgery from the earliest recorded times to the present. He divides it into three sections: The first period is dominated by the ancient Hindu Master of surgery, Susruta, who practiced the couching method of cataract operation several thousand years before Christ. It is interesting to note that some of the pre- and postoperative treatments of Susruta still influence our present views on the handling of cataract patients. The second period starts in 1748 A. D., with the eminent French ophthalmic surgeon, Daviel, who popularized the extracapsular method of cataract extraction. The third period includes the modern times and features mainly the intracapsular method of cataract extraction as described by the leading ophthalmologists of the twentieth century.

The author then continues the second half of the book with a detailed description of the intracapsular cataract extraction; he mentions the pre- and postoperative care—the anesthesia, the surgical techniques, and the handling of the commonly encountered complications. He concludes the book with the treatment of congenital and juvenile cataracts and the various types of complicated cataracts. For this reviewer, however, the main interest of the book lies in its historical aspects, particularly the chapters concerning the ancient Hindu Master, Susruta.

... In Ophthalmic Medication

A PRECEDENT-SETTING INNOVATION

...the 1 cc DROP-TAINER® STERI-UNIT*

Single Dose Disposable Unit with Sterile Outer Surfaces

STERILE • READY FOR USE

*Trade Mark

Patent Pending

Sterile Aqueous Solutions pH and tonicity adjusted preservatives added

Atropine Sulfate 1%

Atropine Sulfate 0.5%

Eserine Salicylate 0.5%

Fluorescein Sod. 2%

Homatropine HBr 5%

Pilocarpine HCl 2%

Sulfacetamide Sod. 15%

Tetracaine HCl 0.5%

plus

Sterile Saline (15cc)

In Boxes of Ten Economically Priced

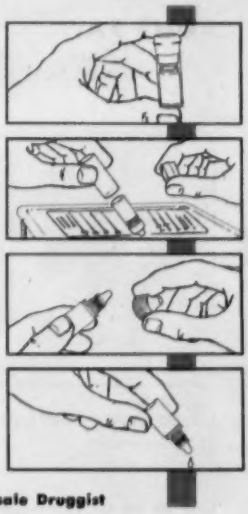
Unsurpassed In Safety and Convenience

1 Drop-Tainer® Steri-Units* may be stored under ordinary conditions and handled freely prior to opening the outer vial without danger of contaminating the sterile surface of the enclosed Drop-Tainer®.

2 The cellulose band and vial closure are removed together by pulling with a slight twist. Care should be exercised so that the fingers do not brush across the open mouth of the vial. The Drop-Tainer® may then be allowed to fall upon the sterile instrument tray by inverting the vial.

3 The entire outer surface of the Drop-Tainer®, as well as its content, is sterile and thus may be safely handled by the surgeon. The cap of the Drop-Tainer® is quickly and easily unscrewed—and the specially designed dropper tip needs no puncturing before use.

4 Gentle pressure on the sides of the Drop-Tainer® will empty its contents in uniform drops; or, rapid squeezing will produce a stream which is sometimes desirable. The solution is preserved and the Drop-Tainer® cap may be replaced for post-operative use of any remaining content.



Now Available From Your Service Wholesale Druggist

For Further Information, Write:

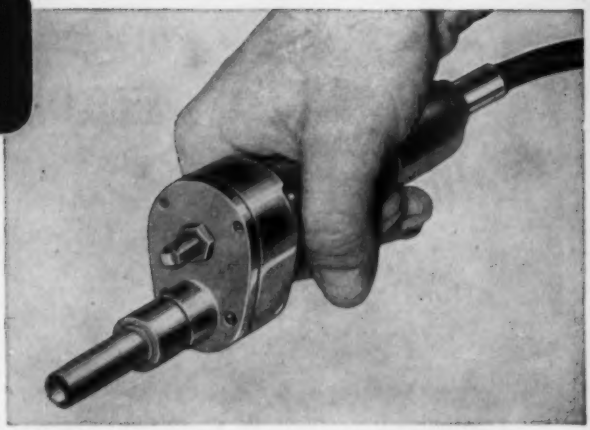
© 1957

Alcon laboratories, inc. • p. o. box 1959 • fort worth, texas

DT SU—1

The Stryker

IMPROVED BONE SAW for the OPHTHALMOLOGIST



. . . is an indispensable aid in performing dacryocystorhinostomies and the Kronlein operation. This efficient bone saw combines these latest refinements developed to best implement the surgeon's skill:

FEATURES of the STRYKER BONE SAW

- LIGHT WEIGHT • MANEUVERABLE
- CONVENIENT TO HOLD • ACCURATE
- VERSATILE • TIME SAVING
- **SAFETY—will not cut or injure the nasal mucus membrane or other adjacent soft tissue.**

Illustrating use of the Iliff Trephine for dacryocystorhinostomies.

Illustrating use of the small sectioned blade in cutting a bony flap in the lateral orbital wall.

ORTHOPEDIC FRAME COMPANY
420 ALCOTT AVENUE
KALAMAZOO, MICHIGAN

☐ Send me the Ophthalmologist Bone Saw on approval.
☐ Send me a brochure and reprint by Charles E. Iliff, M.D.

Name _____

Address _____

City _____ State _____

PRICE: Ophthalmologist Unit Group No. 4 includes 3 blades and 2 trephines $234.00

Orthopedic ORTHOPEDIC FRAME CO.
Kalamazoo Michigan

Distributed in Canada by: Fisher & Burpo, Ltd., Winnipeg
Exclusive Agent for Export: Schuster & Co., 75 Cliff St., N. Y.

THE STYLIST

AN EYEWEAR SCENE STEALER *whenever and wherever it's worn. The* STYLIST *doesn't blare out to detract from facial character and beauty. Quietly its 1/10 12K engraved simplicity takes over the show. One look and you know it is quality.*

Continental
INDIANAPOLIS

Eyes Made To Order

Walter Melcher is applying color on an artificial eye. He needs the skill of an expert glass blower plus the coloring technique of an artist to match eyes of all shapes and colorings. Fortunately, Walter is heir to 105 years' experience. Our skilled glass and plastic eyemakers have passed along and perfected their technics since 1851. These men visit most areas regularly to make artificial eyes that are perfectly matched for your patients—another reason to call or write our nearest office on your next replacement.

Complete Glass and Plastic Artificial Eye Service

- Made to order
- Selections from stock
- Eyes sent on memorandum same day order received
- Damaged or broken eyes accurately matched
- Fitted to all types of motility implants
- Implants, X-Ray therapy shields, foreign body locators
- Superior Quality—Finest Workmanship

Mager and Gougelman inc.

Serving the Profession Since 1851

30 N. Michigan Ave. Chicago 2, Illinois

510 Madison Ave. New York 22, N. Y.

CLEVELAND DETROIT KANSAS CITY MINNEAPOLIS ST. LOUIS BOSTON PHILADELPHIA PITTSBURGH WASHINGTON

Night Driving Demands Lestra-Lite

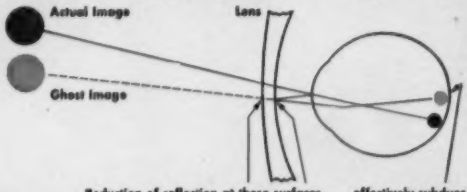
Reg. U.S. Pat. Off.

OPHTHALMIC LENS COATING

"There IS a Difference"

Reflections from eye-glass surfaces are most distracting while driving at night. Light reflected between the front and back lens surfaces and between the cornea and lens surfaces intensifies the glare of oncoming headlights, reducing the driver's visual discrimination. For easier, safer night driving, *always* prescribe Lestra-Lite.

Origin of Ghost Images in a Myopic Eye



Reduction of reflection at these surfaces.....effectively subdues ghost images on retina

FAST LESTRA-LITE SERVICE

Lenses processed and returned postpaid same day as received.

Write for half-coated Lestra-Lite Sample and Literature

PACIFIC UNIVERSAL PRODUCTS CORPORATION

158 Vista Avenue • Pasadena 8, California

130 Bush Street • San Francisco 4, California

THE WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

DEPARTMENT OF OPHTHALMOLOGY

announces its

Thirty-Seventh Annual 8-Month Course In The Basic Sciences Of Ophthalmology

beginning September 16, 1957

1-Week Intensive Course In Pathology Of The Eye And Adnexa

September 30-October 5, 1957

Both courses are limited

A Limited Number of Scholarships are Available

For more detailed information write to:

Department of Ophthalmology
Washington University School of Medicine
St. Louis 10, Missouri

Available...

ISO-SOL®

PROCHELATE

0.37% and 1.85% Solution

ISO-SOL BRAND OF STERILE

EDATHAMIL DISODIUM SOLUTION

Neutral Disodium Ethylenediaminetetraacetate Solution
(Disodium Salt of E. D. T. A.)

Really Effective!

For removing calcific corneal opacities by chelation

LIME BURNS

PLASTER

CEMENT

LIME Slaked or Powdered

BAND KERATITIS

Available in sterile 100 cc vials

Write for literature

THE ISO-SOL CO., INC., BROOKLYN 17, N. Y.

A DRUG OF CHOICE IN GLAUCOMA THERAPY . . .

OPHTHALMOS

PILOCARPINE HCl.
Solutions
½%—1%—2%—4%

OFFER COMFORT AND CONTINUITY OF THERAPY IN THE TREATMENT OF THE *Glaucomas*

—UNDESIRABLE SIDE EFFECTS VIRTUALLY ELIMINATED—
RAPID PROLONGED ACTION

OPHTHALMOS Sterile Pilocarpine HCl. Solutions are prepared according to the Formulae developed by Robert R. Feinstein Research Associates

Prescribe in original 15cc. Dropper Sealed Bottles obtainable promptly through Prescription Pharmacies everywhere

OPHTHALMOS, INC. **UNION CITY, N. J.**

Distributed in Canada by Professional Sales Corp. • 5333 Queen Mary Road, Montreal 29, Quebec

"LACRILENS"®

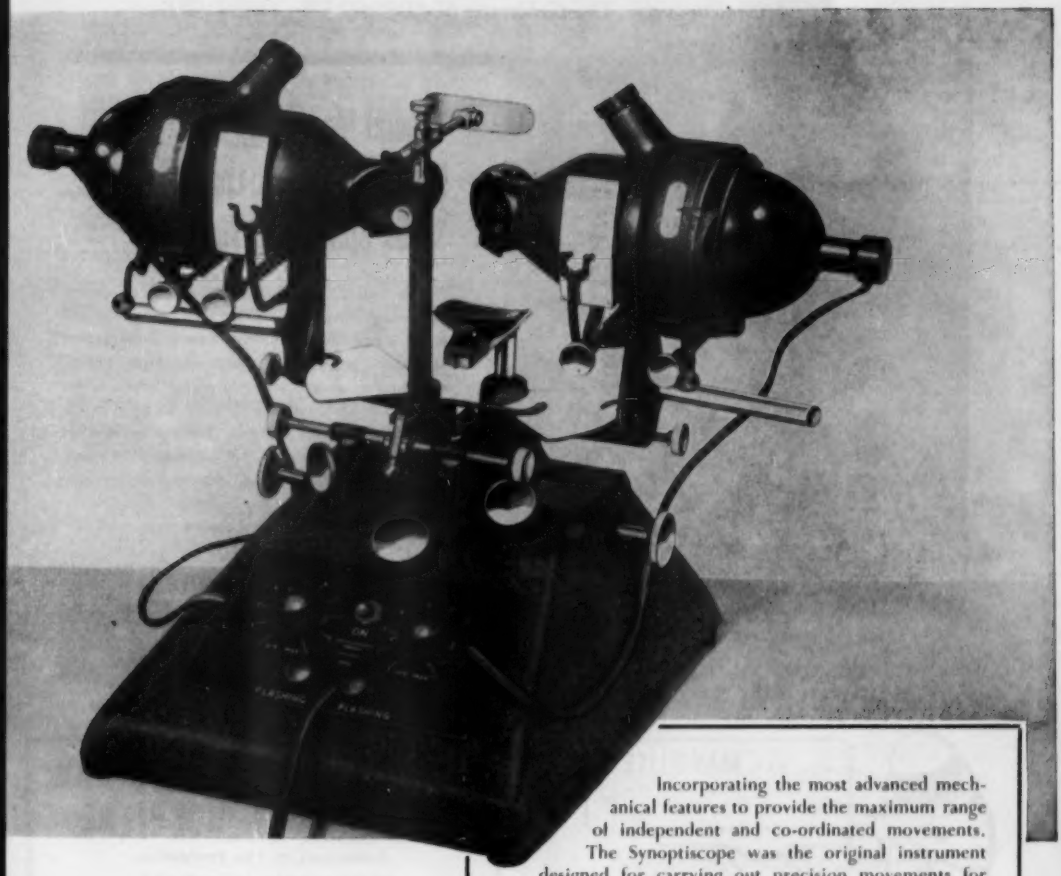
is a safe lens

The test of time proves that the "LACRILENS"® contact lens can be worn for long periods of time in aphakia and in all sports, including swimming. *Write For Brochure*

Obrig Laboratories Inc.
49 East 51st Street, New York 22, N. Y.

Manufacturers of all types of Contact Lenses
Branches in
PHILADELPHIA • MONTREAL • JOHANNESBURG

Obrig®



THE SYNOPTISCOPE by CURRY & PAXTON

INCORPORATED

866 WILLIS AVENUE, ALBERTSON
LONG ISLAND, N. Y.

Telephone: PIONEER 6-0254
Showrooms Service and Assembly Plant

Manufacturers' Representatives in the U. S. A.
Registered Office: 230 Park Avenue New York 17, N. Y.
Telephone Lexington 2-7842

Incorporating the most advanced mechanical features to provide the maximum range of independent and co-ordinated movements. The Synoptiscope was the original instrument designed for carrying out precision movements for Orthoptic training.

MAIN FEATURES

1 **New wide field** eye pieces and larger mirrors, brighter illumination with high intensity gas filled bulbs. 2. **Accurate measurement** of horizontal ductions, vertical ductions and cyclo ductions under the stimulus of Stereoscopic vision or otherwise. 3. **Precise, controlled and unrestricted** exercise of the external ocular motor muscles. *(This function is of especial value where the correcting lenses are not readily accepted by the patient, or where it is required to build up a duction reserve).* 4. **Relaxation exercises.** 5. **Treatment of squint,** including: development of simultaneous macular preception; development of fusion; development of stereoscopic vision and fusional reserve; co-ordination of hand and eye; co-ordinating eye movements.

SUPPLEMENTARY FEATURE
Streak slides for the Bielschowsky after image test.

Other Ophthalmic Instruments manufactured by Curry & Paxton of England include:

SLIT LAMPS • OPHTHALMOSCOPES • THE FOVEOSCOPE • STREAK RETINOSCOPES • MADDOX WING TEST • MADDOX HAND FRAME DIPLOSCOPE • CHEIROSCOPE • TRIAL FRAMES • TRIAL CASES ORTHOPTIC APPARATUS

DISTRIBUTORS: *Chicago*: House of Vision *Los Angeles*: Spratt Optical Superior Optical *San Francisco*: Parsons Laboratories *Pittsburgh*: Doig Optical

Instruments of ophthalmology: The Goldmann Slit Lamp

Special Mounting Of Goldmann Slit Lamp Saves Space and Time

Now the famous Goldmann Slit Lamp becomes even more convenient with Parsons' spring-balanced heavy duty mounting. This mounting swings the slit lamp before the patient instantly, without wheeling or turning knobs to adjust height. Other units, such as a refractor may be mounted on the same base and swung into position as the slit lamp is turned away. The Goldmann Slit Lamp is known for its outstanding design and performance. Write for prices of the Goldmann Slit Lamp, accessories, and Parsons' swing mounting units.

Write: Dept. 6, 518 Powell St.
San Francisco, California

Parsons Optical
LABORATORIES

If You Wear Glasses and Drive at Night

Notice how reflections from electric signs, street lights and headlights on the surfaces of your glasses are very annoying? These are "ghost images" that hamper clear vision and add to the chore of night driving.

MAY-O-LITE, a hard, durable, thin film of Magnesium Fluoride, helps make night driving easier.

Complete Your Professional Service By Adding

The Best in Sight
MAY-O-LITE
Low Reflection Coating

MAY RESEARCH, INC., Box 1181, Minneapolis 1, Minn.

GILL MEMORIAL EYE, EAR, AND THROAT HOSPITAL

Announces to the Profession

THIRTIETH ANNUAL SPRING CONGRESS

in

OPHTHALMOLOGY AND OTOLARYNGOLOGY
April 1st, to April 6th, 1957

GUEST SPEAKERS

Seymour Alpert, M.D.	Washington, D. C.
Edward A. Carr, Jr., M.D.	Ann Arbor, Mich.
James H. Doggart, M.D.	London, England
Harold F. Falls, M.D.	Ann Arbor, Mich.
Frederick A. Figi, M.D., F.A.C.S.	Rochester, Minn.
Samuel Fomon, M.D.	New York, N. Y.
Dan M. Gordon, M.D., F.A.C.S.	New York, N. Y.
Elmer Hess, M.D., F.A.C.S.	Erie, Pa.
Maynard Hine, M.D.	Indianapolis, Ind.
Howard P. House, M.D., F.A.C.S.	Los Angeles, Calif.
Jay G. Linn, Jr., M.D., F.A.C.S.	Pittsburgh, Pa.
Frank W. Newell, M.D., F.A.C.S.	Chicago, Ill.
Hugh L. Ormsby, M.D.	Toronto, Canada
Harry L. Rogers, M.D., F.A.C.S.	Philadelphia, Pa.
Albert D. Ruedemann, M.D., F.A.C.S.	Detroit, Mich.
Frank B. Walsh, M.D.	Baltimore, Md.
Barnes Woodhall, M.D., F.A.C.S.	Durham, N. C.

For Further Information Write:

Superintendent, P. O. Box 1789 Roanoke, Va.

URGENT REQUEST

The Uveitis Laboratory, University of California School of Medicine, San Francisco, is interested to obtain freshly enucleated eyes from patients with *all types of uveitis* and other endogenous inflammations. Attempts are being made to isolate etiologic agents from these eyes.

The eyes should *not* be fixed in preservatives or frozen, but placed in a sterile bottle, packaged, and shipped as quickly as possible. Please send specimens air express, special delivery, *collect*. Enclose history and findings and mark the package "Fresh Tissue Specimen—Rush."

A report of isolations of organisms and pathologic findings, including a slide, will be sent to the contributor. Credit will be given in any resulting publications if desired.

Telegraph collect if specimen being sent.

Send eyes to

Samuel Kimura, M.D., Michael J. Hogan, M.D., or
Phillips Thygeson, M.D.

University of California School of Medicine

San Francisco 22

Here are several booklets on mental hygiene that may prove of interest and use to you and your patients.

EMOTIONAL HEALTH IN WORK AND PLAY
T. R. Retlaw, 8 pages, 15 cents

HYPNOTISM—HUMBUG OR HEALING
James A. Brussel, 6 pages, 10 cents

YOUR STAKE IN MENTAL HEALTH
George S. Stevenson, 4 pages, 10 cents

THE PSYCHIATRIST Edward Dengrove and Doris Kulman, 6 pages, 10 cents

BOOKLETS ON MENTAL HYGIENE

Keep a supply of these booklets on hand. Available at lower cost for quantity purchases.

AMERICAN MEDICAL ASSOCIATION
535 North Dearborn Street • Chicago 10 • Illinois

A foremost specialist says:

"This tells me what the strabismic can do!--

"Now I can tell, right at the start, whether there's a good chance to handle the case successfully by orthoptics.

"I begin by finding immediately the stage at which the strabismic is operating visually.

"The strabismic hasn't had a fair chance in the past— he has been diagnosed on equipment limited to a 20° field.

"But many strabismics who lack macular fusion will show third degree fusion at 30° to 40° or beyond — nearly all strabismics with normal correspondence have third degree fusion. *With Keystone Colordepth Equipment I can probe for fusion as far as 60° peripherally.*"

The Diagnostic Unit may be bought separately if desired. The complete Training Unit also contains the Diagnostic Techniques, so you should examine both.

KEYSTONE VIEW CO., MEADVILLE, PA.

( ) Please send new Bulletin showing how Strabismus is diagnosed and treated with Keystone Colordepth Techniques.

( ) Write or phone me to arrange for demonstration in my office.

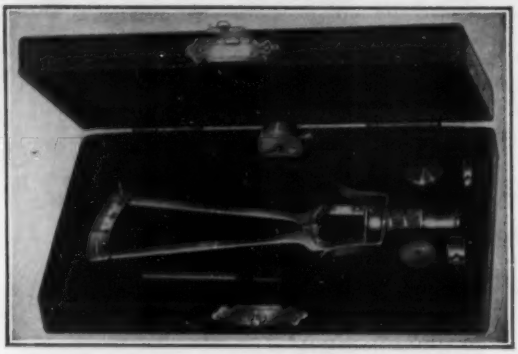
(Name) _____

(Address) _____

E. B. Meyrowitz

SURGICAL INSTRUMENTS CO., INC.,
520 FIFTH AVENUE, NEW YORK 36, N. Y.

LONDON *ESTABLISHED 1875* PARIS



SCHIOTZ ONOMETER

IN STAINLESS STEEL

This instrument is made in strict accordance with the revised specifications adopted on March 8, 1952, by the Committee on Standardization of Tonometers of the American Academy of Ophthalmology and Otolaryngology, and is supplied in a dust-proof case which has separate recesses for the Instrument, Test Block, Weights, and Plunger.
As made in our own laboratories it preserves all of its original effectiveness for determining ocular tension with a new margin of accuracy, sturdiness, ease of handling and beauty of finish that is characteristic of instruments made by Meyrowitz.
It has been found satisfactory by many Ophthalmologists and meets all the specifications of the A.A.O.O. Tonometry Committee.
Approved by the Electrical Testing Laboratories, it leaves nothing to be desired from the standpoint of accuracy.

In case, with certification, each $55.00

WHEN YOUR DIAGNOSIS INDICATES

ORTHOPTICS

IN THE HOME

CONSIDER OUR SALES RECORD OF OVER 11,000 SETS OF

DVORINE ANIMATED FUSION CHARTS

A complete set of fusion charts in full color for office and home training, Base-in and Base-out.

OUTSTANDING FEATURES

- Animation
- Gay Colors
- Duo-Chrome Spectacles and Drawing Outfit
- Nine Groups of Charts
- Vertical Fusion Device
- Tracing Sheets

ALL IN ONE SET
with directions
$12.00
Less 5% if check accompanies your order

Available on prescription at your Ophthalmic Dispenser, American Optical Co., and other optical supply houses.

SCIENTIFIC PUBLISHING CO.
Dept. A—2328 Kutaw Place Baltimore 17, Maryland

POSTGRADUATE

CONFERENCE IN OPHTHALMOLOGY

UNIVERSITY OF MICHIGAN MEDICAL SCHOOL

The Department of Postgraduate Medicine of the University of Michigan Medical School announces the annual conference in Ophthalmology for qualified physicians, April 22, 23 and 24, 1957, to be given at the Horace H. Rackham Graduate School Building, Ann Arbor, Michigan, under the direction of the Department of Ophthalmology.

GUEST LECTURERS

Dr. Arthur Jampolsky, San Francisco, California; Dr. John Clement McCulloch, Toronto, Ontario; Dr. Frank W. Newell, Chicago, Illinois; Dr. Theodore F. Schlaegel, Jr., Indianapolis, Indiana; Dr. Lorenz E. Zimmerman, Washington, D. C.

MEMBERS OF STAFF

Dr. F. Bruce Fralick, Dr. Harold F. Falls, Dr. John W. Henderson, Dr. John W. Smillie, and Dr. J. Reimer Wolter.

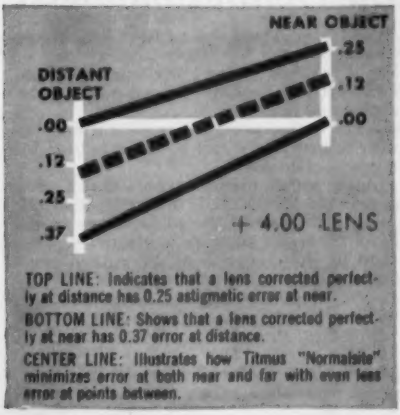
Complete program and details will be mailed upon request.

John M. Sheldon, M.D., Director
Department of Postgraduate Medicine
Room 1610 University Hospital
Ann Arbor, Michigan

Titmus NORMALSITE®

designed to minimize
marginal astigmatism at **both far and near**

offering comfortable vision
over the **entire visual range**



TOP LINE: Indicates that a lens corrected perfectly at distance has 0.25 astigmatic error at near.

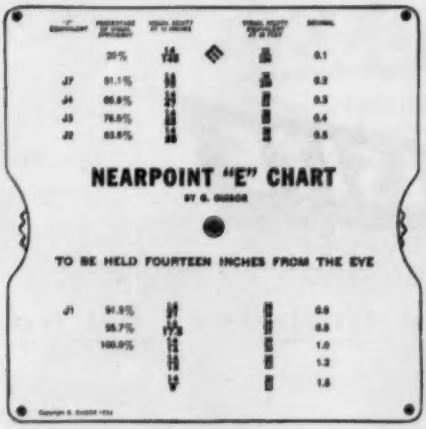
BOTTOM LINE: Shows that a lens corrected perfectly at near has 0.37 error at distance.

CENTER LINE: Illustrates how Titmus "Normalsite" minimizes error at both near and far with even less error at points between.

The Normalsite Single Vision Lens functions like the "normal" eye, producing marginal images of equal sharpness for both near and distant objects.

Titmus OPTICAL COMPANY, INC.
PETERSBURG, VIRGINIA

MANUFACTURERS OF OPHTHALMIC LENSES...FRAMES...SUN GLASSES



New Near Chart

GUIBOR Symbol Near Chart now available in durable and soilproof plastic. Gives distance equivalents, as well as quantitative measurements for near vision. E Symbol understood by all.

Place your order now.

$3.25

DISPENSING SERVICE

Main Office:
111 N. Wabash Ave., at Wash.
Chicago, Illinois

Austin Belgard INC.

OPHTHALMIC OPTICIANS

WHOLESALE & SERVICE

Branch Office:
1139 Central Ave., Wilmette, Ill.

WESLEY CONTACT W/J LENSES JESSEN

Services to the Ophthalmologist

In the past four or five years tremendous strides have been made in the field of contact lenses.

The use of contact lenses for monocular aphakic cases alone would justify the study and fitting of contact lenses, not to mention the need of binocular aphakic cases.

To employ contact lenses as a diagnostic instrument is an aid. Keratoconus and irregular cornea cases can be often helped by the proper utilization of contact lenses.

Other uses of fitting contact lenses include: cases of distorted and discolored eyes (with cosmetic contact lenses); special activities, such as sports, in which normal spectacle lenses would be a handicap and dangerous; various subnormal vision cases . . . contact lenses can be used as the objective in the optical combination to create magnification.

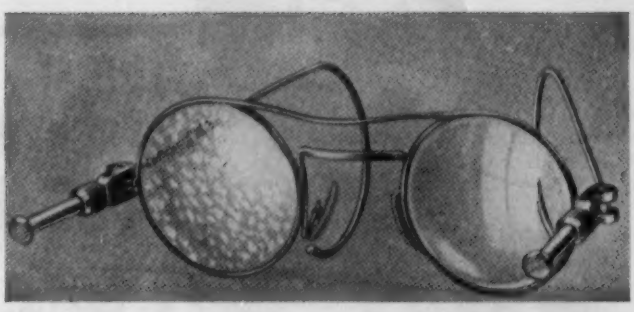
The use of contact lenses for cosmetic purposes cannot be overlooked. There are many other applications for fitting contact lenses.

A knowledge of the various contact lenses should be a part of every ophthalmologist's practice.

Write us for descriptive literature and instructional material on the fitting of Wesley-Jessen contact lenses

THE PLASTIC CONTACT LENS COMPANY 59 E. MADISON ST. CHICAGO 2, ILLINOIS

GOOD NEWS for the sub-normal visioned.



i-gard ASPHERICAL

HYPEROCULAR SPECTACLE MAGNIFIERS

I-GARD Plastic Hyperoculars, new high-powered lenticular lenses worn monocularly in a spectacle frame, offer your handicapped patients these 5 important advantages not obtainable in other types of magnifiers.

BEST GLASS 8x MAGNIFIER

8x I-GARD HYPEROCULAR

CLEARER VISION. Aspherical curvatures, not available in glass (spherical) magnifiers, permit larger magnification with minimum sacrifice of field and definition. *See comparison chart.*

CONTROLLED WORKING DISTANCE. The problem of critical reading distance is solved by adjustable distancing posts against which reading matter is held. When not in use, the posts fold back.

IMPROVED APPEARANCE. The apertures of the 4x, 6x and 8x lenses are 40, 36 and 34 mm. respectively. The lenses can be glazed to cosmetic size.

EXTREME LIGHT WEIGHT. The 8x lens weighs less than ⅛ oz. (8 grams)!

PRICELESS PROTECTION — due to the high resistance to impact of I-Gard plastic.

ORDER TESTING SET NOW

For booklet and name of nearest I-Gard Distributor, write
Dept. E
McLEOD OPTICAL CO., INC.
357 Westminster Street
Providence 1, R. I.

Testing Set

The I-Gard Hyperocular Testing Set contains *(a)* three I-Gard Hyperocular lenses glazed to 40 mm. trial rims to permit maximum field. *(b)* a specially designed single celled trial frame with adjustable distancing posts, *(c)* an occluding disc. Complete with case.

THE M-1 STRONTIUM-90 APPLICATOR

For treatment of superficial corneal diseases by beta radiation

Our booklet, "Radiation Therapy Sources," offers valuable data on beta radiation treatment which will be of interest to you. It includes clinical data, indications for treatment by irradiation, suggested dosage table, U. S. Atomic Energy Commission regulations, and a description of our improved M-1 Applicator.

Write for it today. It is yours free of charge or obligation.

Armamentarium

V MUELLER & CO.

330 South Honore Street
Chicago 12, Illinois

DALLAS • HOUSTON • LOS ANGELES • ROCHESTER, MINN.

---

an answer to **LOW VISUAL ACUITY**

Spectel
TELESCOPIC SPECTACLES

Experience has shown that Spectel Telescopic Spectacles effect substantial improvement in many cases of low visual acuity. Available in two powers, Spectels provide retinal image magnification of 1.7 and 2.2 diameters.

Prescribing Spectel Telescopic Spectacles is primarily an extension of regular refracting routine. Trial sets are simple to use and moderate in price.

Full details in Bulletin 302 available from your supply house or direct from us.

2.2x (with Coated Lenses)

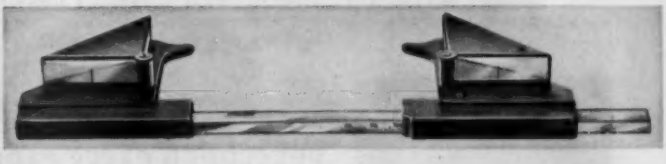
KOLLMORGEN *Optical* **CORPORATION**

NORTHAMPTON, MASSACHUSETTS

Distributed in Canada by Imperial Optical Company

K C

storz
Surgical Instruments



Hertel Exophthalmometer

PRISMATIC

E-5980 Exophthalmometer, Hertel: prismatic, facilitates measuring accurately and rapidly without assistance the degree of exophthalmos. Use of etched prisms results in a permanent instrument not subject to mirror deterioration found in reflecting types $64.50

Ocular Coagulator

E-915 Cautery, Ocular, Hildreth: new model for medium "C" size photo flash battery complete with battery and two electrodes. Sufficient heat for most ocular surgical requirements yet delicate enough for careful application in glaucoma and cataract surgery to overcome troublesome oozing. A self-contained cautery, small, compact, easy to handle. Eliminates troublesome cords and transformers and the danger of open flame. Heats instantly. Duration medium "C" size photo flash battery is sufficient for normal use in several operations. Ref. Am. Journal Ophthalmology, May 1951, Page 750. $17.50
E-922 Electrode, Ocular, Cautery: round, for No. E-915 . . . . $2.50
E-924 Electrode, Ocular, Cautery: pointed, for No. E-915 . . . $2.50

Storz Instruments are available from Storz Salesmen only. We do not distribute under any other name or trademark.

The 1957 Supplement to our Eye Instrument Catalogue has just been issued with listings of new developments. Sent upon request.

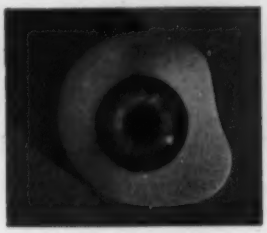
Storz Instrument Company

4570 Audubon Avenue **Saint Louis 10, Missouri**

Specialists in ALL TYPES of Plastic and Glass Artificial Human Eyes Exclusively

MADE TO ORDER IN OUR OWN LABORATORY

Doctors are invited to visit



PREFERRED CASES CAREFULLY ATTENDED AND SATISFACTION GUARANTEED

EYES ALSO FITTED FROM STOCK

Plastic or Glass Selections Sent on Memorandum upon Request

Implants and Plastic Conformers in Stock

FRIED AND KOHLER, INC.

665 FIFTH AVENUE near 53rd St.

NEW YORK, N. Y. Tel. ELdorado 5-1970

Rx

QUALITY SERVICE

Technical skills and services that will never let you down

DOW

Top-Grade Technical Performance

. . . a Safeguard for Your Professional Skills and Judgment.

¶Your prescriptions, conceived from your rich fund of scientific knowledge laboriously developed through years of study, training and experience, are at the mercy of the dispensers who interpret them. They will be safe in the hands of Dow seasoned craftsmen, whose devotion to the exacting standards which your professional reputation demands, and which our firm has consistently maintained throughout its 31 years of existence, is a guarantee of complete patient satisfaction.

DOW OPTICAL CO.

W. E. DOW, Pres.

Chicago, Ill. Bloomington, Ill.

CASE HISTORY #2

This second case history involving the use of CATAREX T temporary cataract bifocal lenses demonstrates that CATAREX T can be prescribed for and worn to advantage by the patient as early as ten days after cataract surgery.

This advantage is, of course, immeasurably valuable in cases where the patient, by virtue of financial circumstances, must be back on the job as soon as possible.

Catarex Service, when used in conjunction with CATAREX D permanent bifocals, may prove to be useful in *your* practice . . . why not check with your laboratory or optician?

CASE HISTORY – Mrs. X. X.

The patient, a female 68 years of age, was first seen on January 8, 1953, and a diagnosis of right senile cataract was made. The left eye was painful and blind. One week later, an alcohol injection about the left ciliary ganglion relieved the patient of pain and enabled her to retain the eye, which was psychologically most desirable.

On May 18, 1954, a right intracapsular lens extraction was performed without complication. The post-operative course was uneventful and the patient was discharged from the hospital on May 27th. While the patient was still in the hospital, a +10.00D temporary single-vision* lens was ordered and fitted on the patient's first office visit on May 28th. With this lens, the right vision = 20/50.

6-9-54: Manifest O.D. +11.00Dsph. ○ +2.50Dcyl. ax 10 = 20/30—. Rx Right: this in CATAREX T (temporary style) straight-top bifocal. Left: lens to balance. The patient was allowed to retain the previous lens until the new CATAREX T bifocal was received. This plan was followed on all subsequent changes.

7-8-54: Manifest O.D. +11.50Dsph. ○ +1.50Dcyl. ax 15 = 20/25+. Rx Right: this in CATAREX T. Left: lens to balance.

8-9-54: Manifest O.D. +12.00Dsph. ○ +1.25Dcyl. ax 15 = 20/15. Rx Right: this in CATAREX D permanent bifocal. Left: lens to balance.

1-25-56: Sixteen months after securing the permanent CATAREX D bifocal, the Right vision with this lens = 20/15.

This patient, who secured her first CATAREX T (temporary style) lens ten days after cataract surgery and had three different changes, secured her first and only permanent lens approximately four months after surgery. To date, she has not had to have it changed or re-surfaced.

**Single-vision CATAREX T.*

CATAREX 'T' TEMPORARY CATARACT BIFOCAL LENSES BY **VISION-EASE**

Manufacturers of a complete line of quality multifocals

Partners in the practice of over 100,000 doctors

Dependable, accurate, easy-to-use

WELCH ALLYN

Otoscopes and Ophthalmoscopes